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<b>(21) International Application Number:</b> PCT/GB97/02273 <b>(22) International Filing Date:</b> 22 August 1997 (22.08.97)  <b>(30) Priority Data:</b> 9617671.4                      23 August 1996 (23.08.96)      GB 9625996.5                      13 December 1996 (13.12.96)      GB  <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US    08/782,893 (CIP) Filed on                                      27 December 1996 (27.12.96)  <b>(71) Applicants (for all designated States except US):</b> MICROBIOLOGICAL RESEARCH AUTHORITY CAMR (CENTRE FOR APPLIED MICROBIOLOGY & RESEARCH) [GB/GB]; Porton Down, Salisbury, Wiltshire SP4 0JG (GB). THE SPEYWOOD LABORATORY LIMITED [GB/GB]; 14 Kensington Square, London W8 5HH (GB).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SHONE, Clifford, Charles [GB/GB]; Microbiological Research Authority CAMR (Centre for Applied Microbiology & Research), Porton Down, Salisbury, Wiltshire SP4 0JG (GB). QUINN,		Conrad, Padraig [GB/GB]; Microbiological Research Authority CAMR (Centre for Applied Microbiology & Research), Porton Down, Salisbury, Wiltshire SP4 0JG (GB). FOSTER, Keith, Alan [GB/GB]; Microbiological Research Authority CAMR (Centre for Applied Microbiology & Research), Porton Down, Salisbury, Wiltshire SP4 0JG (GB).  <b>(74) Agent:</b> SCHLICH, George, William; Mathys & Squire, 100 Gray's Inn Road, London WC1X 8AL (GB).  <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.          Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> RECOMBINANT TOXIN FRAGMENTS  <b>(57) Abstract</b> <p>A polypeptide has first and second domains which enable the polypeptide to be translocated into a target cell or which increase the solubility of the polypeptide, or both, and further enable the polypeptide to cleave one or more vesicle or plasma-membrane associated proteins essential to exocytosis. The polypeptide thus combines useful properties of a clostridial toxin, such as a botulinum or tetanus toxin, without the toxicity associated with the natural molecule. The polypeptide can also contain a third domain that targets it to a specific cell, rendering the polypeptide useful in inhibition of exocytosis in target cells. Fusion proteins comprising the polypeptide, nucleic acids encoding the polypeptide and methods of making the polypeptide are also provided. Controlled activation of the polypeptide is possible and the polypeptide can be incorporated into vaccines and toxin assays.</p>		

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## RECOMBINANT TOXIN FRAGMENTS

This invention relates to recombinant toxin fragments, to DNA encoding these fragments and to their uses such as in a vaccine and for *in vitro* and *in vivo* purposes.

The clostridial neurotoxins are potent inhibitors of calcium-dependent neurotransmitter secretion in neuronal cells. They are currently considered to mediate this activity through a specific endoproteolytic cleavage of at least one of three vesicle or pre-synaptic membrane associated proteins VAMP, syntaxin or SNAP-25 which are central to the vesicle docking and membrane fusion events of neurotransmitter secretion. The neuronal cell targeting of tetanus and botulinum neurotoxins is considered to be a receptor mediated event following which the toxins become internalised and subsequently traffic to the appropriate intracellular compartment where they effect their endopeptidase activity.

The clostridial neurotoxins share a common architecture of a catalytic L-chain (LC, ca 50 kDa) disulphide linked to a receptor binding and translocating H-chain (HC, ca 100 kDa). The HC polypeptide is considered to comprise all or part of two distinct functional domains. The carboxy-terminal half of the HC (ca 50 kDa), termed the H<sub>C</sub> domain, is involved in the high affinity, neurospecific binding of the neurotoxin to cell surface receptors on the target neuron, whilst the amino-terminal half, termed the H<sub>N</sub> domain (ca 50 kDa), is considered to mediate the translocation of at least some portion of the neurotoxin across cellular membranes such that the functional activity of the LC is expressed within the target cell. The H<sub>N</sub> domain also has the property, under conditions of low pH, of forming ion-permeable channels in lipid membranes, this may in some manner relate to its translocation function.

For botulinum neurotoxin type A (BoNT/A) these domains are considered to reside within amino acid residues 872-1296 for the H<sub>C</sub>, amino acid residues 449-871 for the H<sub>N</sub> and residues 1-448 for the LC. Digestion with trypsin effectively degrades the H<sub>C</sub> domain of the BoNT/A to generate a non-toxic fragment designated LH<sub>N</sub>.

which is no longer able to bind to and enter neurons (Fig. 1). The LH<sub>N</sub> fragment so produced also has the property of enhanced solubility compared to both the parent holotoxin and the isolated LC.

It is therefore possible to provide functional definitions of the domains within the neurotoxin molecule, as follows:

(A) clostridial neurotoxin light chain:

-a metalloprotease exhibiting high substrate specificity for vesicle and/or plasma - membrane associated proteins involved in the exocytotic process. In particular, it cleaves one or more of SNAP-25, VAMP (synaptobrevin / cellubrevin) and syntaxin.

(B) clostridial neurotoxin heavy chain H<sub>N</sub> domain:

-a portion of the heavy chain which enables translocation of that portion of the neurotoxin molecule such that a functional expression of light chain activity occurs within a target cell.

-the domain responsible for translocation of the endopeptidase activity, following binding of neurotoxin to its specific cell surface receptor via the binding domain, into the target cell.

-the domain responsible for formation of ion-permeable pores in lipid membranes under conditions of low pH.

-the domain responsible for increasing the solubility of the entire polypeptide compared to the solubility of light chain alone.

(C) clostridial neurotoxin heavy chain H<sub>C</sub> domain.

~~-----a portion of the heavy chain which is responsible for binding of the native~~

holotoxin to cell surface receptor(s) involved in the intoxicating action of clostridial toxin prior to internalisation of the toxin into the cell.

The identity of the cellular recognition markers for these toxins is currently not understood and no specific receptor species have yet been identified although Kozaki et al. have reported that synaptotagmin may be the receptor for botulinum neurotoxin type B. It is probable that each of the neurotoxins has a different receptor.

It is desirable to have positive controls for toxin assays, to develop clostridial toxin vaccines and to develop therapeutic agents incorporating desirable properties of clostridial toxin.

However, due to its extreme toxicity, the handling of native toxin is hazardous.

The present invention seeks to overcome or at least ameliorate problems associated with production and handling of clostridial toxin.

Accordingly, the invention provides a polypeptide comprising first and second domains, wherein said first domain is adapted to cleave one or more vesicle or plasma-membrane associated proteins essential to neuronal exocytosis and wherein said second domain is adapted (i) to translocate the polypeptide into the cell or (ii) to increase the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both to translocate the polypeptide into the cell and to increase the solubility of the polypeptide compared to the solubility of the first domain on its own, said polypeptide being free of clostridial neurotoxin and free of any clostridial neurotoxin precursor that can be converted into toxin by proteolytic action. Accordingly, the invention may thus provide a single polypeptide chain containing a domain equivalent to a clostridial toxin light chain and a domain providing the functional aspects of the  $H_N$  of a clostridial toxin heavy chain, whilst lacking the functional aspects of a clostridial toxin  $H_C$  domain.

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For the purposes of the invention, the functional property or properties of the  $H_N$  of a clostridial toxin heavy chain that are required to be exhibited by the second domain of the polypeptide of the invention are either (i) translocation of the polypeptide into a cell, or (ii) increasing solubility of the polypeptide compared to solubility of the first domain on its own or (iii) both (i) and (ii). References hereafter to a  $H_N$  domain or to the functions of a  $H_N$  domain are references to this property or properties. The second domain is not required to exhibit other properties of the  $H_N$  domain of a clostridial toxin heavy chain.

A polypeptide of the invention can thus be soluble but lack the translocation function of a native toxin-this is of use in providing an immunogen for vaccinating or assisting to vaccinate an individual against challenge by toxin. In a specific embodiment of the invention described in an example below a polypeptide designated LH<sub>423</sub>/A elicited neutralising antibodies against type A neurotoxin. A polypeptide of the invention can likewise thus be relatively insoluble but retain the translocation function of a native toxin - this is of use if solubility is imparted to a composition made up of that polypeptide and one or more other components by one or more of said other components.

The first domain of the polypeptide of the invention cleaves one or more vesicle or plasma-membrane associated proteins essential to the specific cellular process of exocytosis, and cleavage of these proteins results in inhibition of exocytosis, typically in a non-cytotoxic manner. The cell or cells affected are not restricted to a particular type or subgroup but can include both neuronal and non-neuronal cells. The activity of clostridial neurotoxins in inhibiting exocytosis has, indeed, been observed almost universally in eukaryotic cells expressing a relevant cell surface receptor, including such diverse cells as from *Aplysia* (sea slug), *Drosophila* (fruit fly) and mammalian nerve cells, and the activity of the first domain is to be understood as including a corresponding range of cells.

The polypeptide of the invention may be obtained by expression of a recombinant ~~nucleic acid, preferably a DNA, and is a single polypeptide, that is to say not~~

cleaved into separate light and heavy chain domains. The polypeptide is thus available in convenient and large quantities using recombinant techniques.

In a polypeptide according to the invention, said first domain preferably comprises a clostridial toxin light chain or a fragment or variant of a clostridial toxin light chain. The fragment is optionally an N-terminal, or C-terminal fragment of the light chain, or is an internal fragment, so long as it substantially retains the ability to cleave the vesicle or plasma-membrane associated protein essential to exocytosis. The minimal domains necessary for the activity of the light chain of clostridial toxins are described in J. Biol. Chem., Vol.267, No. 21, July 1992, pages 14721-14729. The variant has a different peptide sequence from the light chain or from the fragment, though it too is capable of cleaving the vesicle or plasma-membrane associated protein. It is conveniently obtained by insertion, deletion and/or substitution of a light chain or fragment thereof. In embodiments of the invention described below a variant sequence comprises (i) an N-terminal extension to a clostridial toxin light chain or fragment (ii) a clostridial toxin light chain or fragment modified by alteration of at least one amino acid (iii) a C-terminal extension to a clostridial toxin light chain or fragment, or (iv) combinations of 2 or more of (i)-(iii).

In further embodiments of the invention, the variant contains an amino acid sequence modified so that (a) there is no protease sensitive region between the LC and H<sub>N</sub> components of the polypeptide, or (b) the protease sensitive region is specific for a particular protease. This latter embodiment is of use if it is desired to activate the endopeptidase activity of the light chain in a particular environment or cell. Though, in general, the polypeptides of the invention are activated prior to administration.

The first domain preferably exhibits endopeptidase activity specific for a substrate selected from one or more of SNAP-25, synaptobrevin/VAMP and syntaxin. The clostridial toxin is preferably botulinum toxin or tetanus toxin.

In an embodiment of the invention described in an example below, the toxin light

chain and the portion of the toxin heavy chain are of botulinum toxin type A. In a further embodiment of the invention described in an example below, the toxin light chain and the portion of the toxin heavy chain are of botulinum toxin type B. The polypeptide optionally comprises a light chain or fragment or variant of one toxin type and a heavy chain or fragment or variant of another toxin type.

In a polypeptide according to the invention said second domain preferably comprises a clostridial toxin heavy chain  $H_N$  portion or a fragment or variant of a clostridial toxin heavy chain  $H_N$  portion. The fragment is optionally an N-terminal or C-terminal or internal fragment, so long as it retains the function of the  $H_N$  domain. Teachings of regions within the  $H_N$  responsible for its function are provided for example in Biochemistry 1995, 34, pages 15175-15181 and Eur. J. Biochem, 1989, 185, pages 197-203. The variant has a different sequence from the  $H_N$  domain or fragment, though it too retains the function of the  $H_N$  domain. It is conveniently obtained by insertion, deletion and/or substitution of a  $H_N$  domain or fragment thereof. In embodiments of the invention, described below, it comprises (i) an N-terminal extension to a  $H_N$  domain or fragment, (ii) a C-terminal extension to a  $H_N$  domain or fragment, (iii) a modification to a  $H_N$  domain or fragment by alteration of at least one amino acid, or (iv) combinations of 2 or more of (i)-(iii). The clostridial toxin is preferably botulinum toxin or tetanus toxin.

The invention also provides a polypeptide comprising a clostridial neurotoxin light chain and a N-terminal fragment of a clostridial neurotoxin heavy chain, the fragment preferably comprising at least 423 of the N-terminal amino acids of the heavy chain of botulinum toxin type A, 417 of the N-terminal amino acids of the heavy chain of botulinum toxin type B or the equivalent number of N-terminal amino acids of the heavy chain of other types of clostridial toxin such that the fragment possesses an equivalent alignment of homologous amino acid residues.

These polypeptides of the invention are thus not composed of two or more polypeptides, linked for example by di-sulphide bridges into composite molecules. ~~Instead, these polypeptides are single chains and are not active or their activity is~~



significantly reduced in an *in vitro* assay of neurotoxin endopeptidase activity.

Further, the polypeptides may be susceptible to be converted into a form exhibiting endopeptidase activity by the action of a proteolytic agent, such as trypsin. In this way it is possible to control the endopeptidase activity of the toxin light chain.

In a specific embodiment of the invention described in an example below, there is provided a polypeptide lacking a portion designated H<sub>C</sub> of a clostridial toxin heavy chain. This portion, seen in the naturally produced toxin, is responsible for binding of toxin to cell surface receptors prior to internalisation of the toxin. This specific embodiment is therefore adapted so that it can not be converted into active toxin, for example by the action of a proteolytic enzyme. The invention thus also provides a polypeptide comprising a clostridial toxin light chain and a fragment of a clostridial toxin heavy chain, said fragment being not capable of binding to those cell surface receptors involved in the intoxicating action of clostridial toxin, and it is preferred that such a polypeptide lacks an intact portion designated H<sub>C</sub> of a clostridial toxin heavy chain.

In further embodiments of the invention there are provided compositions containing a polypeptide comprising a clostridial toxin light chain and a portion designated H<sub>N</sub> of a clostridial toxin heavy chain, and wherein the composition is free of clostridial toxin and free of any clostridial toxin precursor that may be converted into clostridial toxin by the action of a proteolytic enzyme. Examples of these compositions include those containing toxin light chain and H<sub>N</sub> sequences of botulinum toxin types A, B, C<sub>1</sub>, D, E, F and G.

The polypeptides of the invention are conveniently adapted to bind to, or include, a ligand for targeting to desired cells. The polypeptide optionally comprises a sequence that binds to, for example, an immunoglobulin. A suitable sequence is a tandem repeat synthetic IgG binding domain derived from domain B of Staphylococcal protein A. Choice of immunoglobulin specificity then determines the target for a polypeptide - immunoglobulin complex. Alternatively, the

polypeptide comprises a non-clostridial sequence that binds to a cell surface receptor, suitable sequences including insulin-like growth factor-1 (IGF-1) which binds to its specific receptor on particular cell types and the 14 amino acid residue sequence from the carboxy-terminus of cholera toxin A subunit which is able to bind the cholera toxin B subunit and thence to GM1 gangliosides. A polypeptide according to the invention thus, optionally, further comprises a third domain adapted for binding of the polypeptide to a cell.

In a second aspect the invention provides a fusion protein comprising a fusion of (a) a polypeptide of the invention as described above with (b) a second polypeptide adapted for binding to a chromatography matrix so as to enable purification of the fusion protein using said chromatography matrix. It is convenient for the second polypeptide to be adapted to bind to an affinity matrix, such as a glutathione Sepharose, enabling rapid separation and purification of the fusion protein from an impure source, such as a cell extract or supernatant.

One possible second purification polypeptide is glutathione-S-transferase (GST), and others will be apparent to a person of skill in the art, being chosen so as to enable purification on a chromatography column according to conventional techniques.

As noted above, by proteolytic treatment, for example using trypsin, of a polypeptide of the invention it is possible to induce endopeptidase activity in the treated polypeptide. A third aspect of the invention provides a composition comprising a derivative of a clostridial toxin, said derivative retaining at least 10% of the endopeptidase activity of the clostridial toxin, said derivative further being non-toxic *in vivo* due to its inability to bind to cell surface receptors, and wherein the composition is free of any component, such as toxin or a further toxin derivative, that is toxic *in vivo*. The activity of the derivative preferably approaches that of natural toxin, and is thus preferably at least 30% and most preferably at least 60% of natural toxin. The overall endopeptidase activity of the composition will, of course, also be determined by the amount of the derivative that is present.

While it is known to treat naturally produced clostridial toxin to remove the H<sub>C</sub> domain, this treatment does not totally remove toxicity of the preparation, instead some residual toxin activity remains. Natural toxin treated in this way is therefore still not entirely safe. The composition of the invention, derived by treatment of a pure source of polypeptide advantageously is free of toxicity, and can conveniently be used as a positive control in a toxin assay, as a vaccine against clostridial toxin or for other purposes where it is essential that there is no residual toxicity in the composition.

The invention enables production of the polypeptides and fusion proteins of the invention by recombinant means.

A fourth aspect of the invention provides a nucleic acid encoding a polypeptide or a fusion protein according to any of the aspects of the invention described above.

In one embodiment of this aspect of the invention, a DNA sequence provided to code for the polypeptide or fusion protein is not derived from native clostridial sequences, but is an artificially derived sequence not preexisting in nature.

A specific DNA (SEQ ID NO: 1) described in more detail below encodes a polypeptide or a fusion protein comprising nucleotides encoding residues 1-871 of a botulinum toxin type A. Said polypeptide comprises the light chain domain and the first 423 amino acid residues of the amino terminal portion of a botulinum toxin type A heavy chain. This recombinant product is designated LH<sub>423</sub>/A (SEQ ID NO: 2).

In a second embodiment of this aspect of the invention a DNA sequence which codes for the polypeptide or fusion protein is derived from native clostridial sequences but codes for a polypeptide or fusion protein not found in nature.

A specific DNA (SEQ ID NO: 19) described in more detail below encodes a polypeptide or a fusion protein and comprises nucleotides encoding residues 1-

1171 of a botulinum toxin type B. Said polypeptide comprises the light chain domain and the first 728 amino acid residues of the amino terminal protein of a botulinum type B heavy chain. This recombinant product is designated LH<sub>728</sub>/B (SEQ ID NO: 20).

The invention thus also provides a method of manufacture of a polypeptide comprising expressing in a host cell a DNA according to the third aspect of the invention. The host cell is suitably not able to cleave a polypeptide or fusion protein of the invention so as to separate light and heavy toxin chains; for example, a non-clostridial host.

The invention further provides a method of manufacture of a polypeptide comprising expressing in a host cell a DNA encoding a fusion protein as described above, purifying the fusion protein by elution through a chromatography column adapted to retain the fusion protein, eluting through said chromatography column a ligand adapted to displace the fusion protein and recovering the fusion protein. Production of substantially pure fusion protein is thus made possible. Likewise, the fusion protein is readily cleaved to yield a polypeptide of the invention, again in substantially pure form, as the second polypeptide may conveniently be removed using the same type of chromatography column.

The LH<sub>N</sub>/A derived from dichain native toxin requires extended digestion with trypsin to remove the C-terminal 1/2 of the heavy chain, the H<sub>C</sub> domain. The loss of this domain effectively renders the toxin inactive *in vivo* by preventing its interaction with host target cells. There is, however, a residual toxic activity which may indicate a contaminating, trypsin insensitive, form of the whole type A neurotoxin.

In contrast, the recombinant preparations of the invention are the product of a discreet, defined gene coding sequence and can not be contaminated by full length toxin protein. Furthermore, the product as recovered from *E. coli*, and from other recombinant expression hosts, is an inactive single chain peptide or if expression

hosts produce a processed, active polypeptide it is not a toxin. Endopeptidase activity of LH<sub>423</sub>/A, as assessed by the current *in vitro* peptide cleavage assay, is wholly dependent on activation of the recombinant molecule between residues 430 and 454 by trypsin. Other proteolytic enzymes that cleave between these two residues are generally also suitable for activation of the recombinant molecule. Trypsin cleaves the peptide bond C-terminal to Arginine or C-terminal to Lysine and is suitable as these residues are found in the 430-454 region and are exposed (see Fig. 12).

The recombinant polypeptides of the invention are potential therapeutic agents for targeting to cells expressing the relevant substrate but which are not implicated in effecting botulism. An example might be where secretion of neurotransmitter is inappropriate or undesirable or alternatively where a neuronal cell is hyperactive in terms of regulated secretion of substances other than neurotransmitter. In such an example the function of the H<sub>C</sub> domain of the native toxin could be replaced by an alternative targeting sequence providing, for example, a cell receptor ligand and/or translocation domain.

One application of the recombinant polypeptides of the invention will be as a reagent component for synthesis of therapeutic molecules, such as disclosed in WO-A-94/21300. The recombinant product will also find application as a non-toxic standard for the assessment and development of *in vitro* assays for detection of functional botulinum or tetanus neurotoxins either in foodstuffs or in environmental samples, for example as disclosed in EP-A-0763131.

A further option is addition, to the C-terminal end of a polypeptide of the invention, of a peptide sequence which allows specific chemical conjugation to targeting ligands of both protein and non-protein origin.

In yet a further embodiment an alternative targeting ligand is added to the N-terminus of polypeptides of the invention. Recombinant LH<sub>N</sub> derivatives have been designated that have specific protease cleavage sites engineered at the C-terminus.

of the LC at the putative trypsin sensitive region and also at the extreme C-terminus of the complete protein product. These sites will enhance the activational specificity of the recombinant product such that the dichain species can only be activated by proteolytic cleavage of a more predictable nature than use of trypsin.

The LH<sub>N</sub> enzymatically produced from native BoNT/A is an efficient immunogen and thus the recombinant form with its total divorce from any full length neurotoxin represents a vaccine component. The recombinant product may serve as a basal reagent for creating defined protein modifications in support of any of the above areas.

Recombinant constructs are assigned distinguishing names on the basis of their amino acid sequence length and their Light Chain (L-chain, L) and Heavy Chain (H-chain, H) content as these relate to translated DNA sequences in the public domain or specifically to SEQ ID NO: 2 and SEQ ID NO: 20. The 'LH' designation is followed by '/X' where 'X' denotes the corresponding clostridial toxin serotype or class, e.g. 'A' for botulinum neurotoxin type A or 'TeTx' for tetanus toxin. Sequence variants from that of the native toxin polypeptide are given in parenthesis in standard format, namely the residue position number prefixed by the residue of the native sequence and suffixed by the residue of the variant.

Subscript number prefixes indicate an amino-terminal (N-terminal) extension, or where negative a deletion, to the translated sequence. Similarly, subscript number suffixes indicate a carboxy terminal (C-terminal) extension or where negative numbers are used, a deletion. Specific sequence inserts such as protease cleavage sites are indicated using abbreviations, e.g. Factor Xa is abbreviated to FXa. L-chain C-terminal suffixes and H-chain N-terminal prefixes are separated by a '/' to indicate the predicted junction between the L and H-chains. Abbreviations for engineered ligand sequences are prefixed or suffixed to the clostridial L-chain or H-chain corresponding to their position in the translation product.

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Following this nomenclature,

- $LH_{423}/A$  = SEQ ID NO: 2, containing the entire L-chain and 423 amino acids of the H-chain of botulinum neurotoxin type A;
- ${}_2LH_{423}/A$  = a variant of this molecule, containing a two amino acid extension to the N-terminus of the L-chain;
- ${}_2L_{1/2}H_{423}/A$  = a further variant in which the molecule contains a two amino acid extension on the N-terminus of both the L-chain and the H-chain;
- ${}_2L_{FXa/2}H_{423}/A$  = a further variant containing a two amino acid extension to the N-terminus of the L-chain, and a Factor Xa cleavage sequence at the C-terminus of the L-chain which, after cleavage of the molecule with Factor Xa leaves a two amino acid N-terminal extension to the H-chain component; and
- ${}_2L_{FXa/2}H_{423}/A\text{-IGF-1}$  = a variant of this molecule which has a further C-terminal extension to the H-chain, in this example the insulin-like growth factor 1 (IGF-1) sequence.

There now follows description of specific embodiments of the invention, illustrated by drawings in which:

Fig. 1 shows a schematic representation of the domain structure of botulinum neurotoxin type A (BoNT/A);

Fig. 2 shows a schematic representation of assembly of the gene for an embodiment of the invention designated  $LH_{423}/A$ ;

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- Fig. 3 is a graph comparing activity of native toxin, trypsin generated "native" LH<sub>N</sub>/A and an embodiment of the invention designated <sub>2</sub>LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y) in an *in vitro* peptide cleavage assay;
- Fig. 4 is a comparison of the first 33 amino acids in published sequences of native toxin and embodiments of the invention;
- Fig. 5 shows the transition region of an embodiment of the invention designated L/<sub>4</sub>H<sub>423</sub>/A illustrating insertion of four amino acids at the N-terminus of the H<sub>N</sub> sequence; amino acids coded for by the *Eco* 47 III restriction endonuclease cleavage site are marked and the H<sub>N</sub> sequence then begins ALN...;
- Fig. 6 shows the transition region of an embodiment of the invention designated L<sub>FXa/3</sub>H<sub>423</sub>/A illustrating insertion of a Factor Xa cleavage site at the C-terminus of the L-chain, and three additional amino acids coded for at the N-terminus of the H-sequence; the N-terminal amino acid of the cleavage-activated H<sub>N</sub> will be cysteine;
- Fig. 7 shows the C-terminal portion of the amino acid sequence of an embodiment of the invention designated L<sub>FXa/3</sub>H<sub>423</sub>/A-IGF-1, a fusion protein; the IGF-1 sequence begins at position G<sub>882</sub>;
- Fig. 8 shows the C-terminal portion of the amino acid sequence of an embodiment of the invention designated L<sub>FXa/3</sub>H<sub>423</sub>/A-CtxA14, a fusion protein; the C-terminal CtxA sequence begins at position Q<sub>882</sub>;
- ~~Fig. 9 shows the C-terminal portion of the amino acid sequence of an~~



embodiment of the invention designated  $L_{FXa/3}H_{423}/A-ZZ$ , a fusion protein; the C-terminal ZZ sequence begins at position  $A_{890}$  immediately after a genenase recognition site (underlined);

show schematic representations of manipulations of

Figs. 10 & 11 polypeptides of the invention; Fig. 10 shows  $LH_{423}/A$  with N-terminal addition of an affinity purification peptide (in this case GST) and C-terminal addition of an Ig binding domain; protease cleavage sites R1, R2 and R3 enable selective enzymatic separation of domains; Fig. 11 shows specific examples of protease cleavage sites R1, R2 and R3 and a C-terminal fusion peptide sequence;

Fig. 12 shows the trypsin sensitive activation region of a polypeptide of the invention;

Fig. 13 shows Western blot analysis of recombinant  $LH_{107}/B$  expressed from *E.coli*; panel A was probed with anti-BoNT/B antiserum; Lane 1, molecular weight standards; lanes 2 & 3, native BoNT/B; lane 4, immunopurified  $LH_{107}/B$ ; panel B was probed with anti-T7 peptide tag antiserum; lane 1, molecular weight standards; lanes 2 & 3, positive control *E.coli* T7 expression; lane 4 immunopurified  $LH_{107}/B$ .

The sequence listing that accompanies this application contains the following sequences:-

SEQ ID NO:

Sequence

1

DNA coding for  $LH_{423}/A$

- 2 LH<sub>423</sub>/A
- 3 DNA coding for <sub>23</sub>LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y), of which an N-terminal portion is shown in Fig. 4.
- 4 <sub>23</sub>LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y)
- 5 DNA coding for <sub>2</sub>LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y), of which an N-terminal portion is shown in Fig. 4
- 6 <sub>2</sub>LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y)
- 7 DNA coding for native BoNT/A according to Binz et al
- 8 native BoNT/A according to Binz et al
- 9 DNA coding for L<sub>/4</sub>H<sub>423</sub>/A
- 10 L<sub>/4</sub>H<sub>423</sub>/A
- 11 DNA coding for L<sub>FXa/3</sub>H<sub>423</sub>/A
- 12 L<sub>FXa/3</sub>H<sub>423</sub>/A
- 13 DNA coding for L<sub>FXa/3</sub>H<sub>423</sub>/A-IGF-1
- 14 L<sub>FXa/3</sub>H<sub>423</sub>/A-IGF-1
- 15 DNA coding for L<sub>FXa/3</sub>H<sub>423</sub>/A-CtxA14
- 16 L<sub>FXa/3</sub>H<sub>423</sub>/A-CtxA14
- 17 DNA coding for L<sub>FXa/3</sub>H<sub>423</sub>/A-ZZ
- 18 L<sub>FXa/3</sub>H<sub>423</sub>/A-ZZ
- 19 DNA coding for LH<sub>728</sub>/B
- 20 LH<sub>728</sub>/B
- 21 DNA coding for LH<sub>417</sub>/B
- 22 LH<sub>417</sub>/B
- 23 DNA coding for LH<sub>107</sub>/B
- 24 LH<sub>107</sub>/B
- 25 DNA coding for LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y)
- 26 LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y)
- ~~27 DNA coding for LH<sub>417</sub>/B wherein the first 274 bases are~~

28 modified to have an *E. coli* codon bias  
DNA coding for LH<sub>417</sub>/B wherein bases 691-1641 of the native BoNT/B sequence have been replaced by a degenerate DNA coding for amino acid residues 231-547 of the native BoNT/B polypeptide

#### Example 1

A 2616 base pair, double stranded gene sequence (SEQ ID NO: 1) has been assembled from a combination of synthetic, chromosomal and polymerase-chain-reaction generated DNA (Figure 2). The gene codes for a polypeptide of 871 amino acid residues corresponding to the entire light-chain (LC, 448 amino acids) and 423 residues of the amino terminus of the heavy-chain (H<sub>C</sub>) of botulinum neurotoxin type A. This recombinant product is designated the LH<sub>423</sub>/A fragment (SEQ ID NO: 2).

#### Construction of the recombinant product

The first 918 base pairs of the recombinant gene were synthesised by concatenation of short oligonucleotides to generate a coding sequence with an *E. coli* codon bias. Both DNA strands in this region were completely synthesised as short overlapping oligonucleotides which were phosphorylated, annealed and ligated to generate the full synthetic region ending with a unique *KpnI* restriction site. The remainder of the LH<sub>423</sub>/A coding sequence was PCR amplified from total chromosomal DNA from *Clostridium botulinum* and annealed to the synthetic portion of the gene.

The internal PCR amplified product sequences were then deleted and replaced with the native, fully sequenced, regions from clones of *C. botulinum* chromosomal origin to generate the final gene construct. The final composition is synthetic DNA (bases 1-913), polymerase amplified DNA (bases 914-1138 and 1976-2616) and the remainder is of *C. botulinum* chromosomal origin (bases 1139-1975). The

assembled gene was then fully sequenced and cloned into a variety of *E.coli* plasmid vectors for expression analysis.

#### Expression of the recombinant gene and recovery of protein product

The DNA is expressed in *E. coli* as a single nucleic acid transcript producing a soluble single chain polypeptide of 99,951 Daltons predicted molecular weight. The gene is currently expressed in *E. coli* as a fusion to the commercially available coding sequence of glutathione S-transferase (GST) of *Schistosoma japonicum* but any of an extensive range of recombinant gene expression vectors such as pEZZ18, pTrc99, pFLAG or the pMAL series may be equally effective as might expression in other prokaryotic or eukaryotic hosts such as the Gram positive bacilli, the yeast *P. pastoris* or in insect or mammalian cells under appropriate conditions.

Currently, *E. coli* harbouring the expression construct is grown in Luria-Bertani broth (L-broth pH 7.0, containing 10 g/l bacto-tryptone, 5 g/l bacto-yeast extract and 10 g/l sodium chloride) at 37° C until the cell density (biomass) has an optical absorbance of 0.4- 0.6 at 600 nm and the cells are in mid-logarithmic growth phase. Expression of the gene is then induced by addition of isopropylthio- $\beta$ -D-galactosidase (IPTG) to a final concentration of 0.5 mM. Recombinant gene expression is allowed to proceed for 90 min at a reduced temperature of 25°C. The cells are then harvested by centrifugation, are resuspended in a buffer solution containing 10 mM Na<sub>2</sub>HPO<sub>4</sub>, 0.5 M NaCl, 10 mM EGTA, 0.25% Tween, pH 7.0 and then frozen at -20°C. For extraction of the recombinant protein the cells are disrupted by sonication. The cell extract is then cleared of debris by centrifugation and the cleared supernatant fluid containing soluble recombinant fusion protein (GST- LH<sub>423</sub>/A) is stored at -20°C pending purification. A proportion of recombinant material is not released by the sonication procedure and this probably reflects insolubility or inclusion body formation. Currently we do not extract this material for analysis but if desired this could be readily achieved using methods known to those skilled in the art.

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The recombinant GST- LH<sub>423</sub>/A is purified by adsorption onto a commercially prepared affinity matrix of glutathione Sepharose and subsequent elution with reduced glutathione. The GST affinity purification marker is then removed by proteolytic cleavage and reabsorption to glutathione Sepharose; recombinant LH<sub>423</sub>/A is recovered in the non-adsorbed material.

#### Construct variants

A variant of the molecule, LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y) (SEQ ID NO: 26) has been produced in which three amino acid residues have been modified within the light chain of LH<sub>423</sub>/A producing a polypeptide containing a light chain sequence different to that of the published amino acid sequence of the light chain of BoNT/A.

Two further variants of the gene sequence that have been expressed and the corresponding products purified are <sub>23</sub>LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y) (SEQ ID NO: 4) which has a 23 amino acid N-terminal extension as compared to the predicted native L-chain of BoNT/A and <sub>2</sub>LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y) (SEQ ID NO: 6) which has a 2 amino acid N-terminal extension (Figure 4).

In yet another variant a gene has been produced which contains a *Eco* 47 III restriction site between nucleotides 1344 and 1345 of the gene sequence given in (SEQ ID NO: 1). This modification provides a restriction site at the position in the gene representing the interface of the heavy and light chains in native neurotoxin, and provides the capability to make insertions at this point using standard restriction enzyme methodologies known to those skilled in the art. It will also be obvious to those skilled in the art that any one of a number of restriction sites could be so employed, and that the *Eco* 47 III insertion simply exemplifies this approach. Similarly, it would be obvious for one skilled in the art that insertion of a restriction site in the manner described could be performed on any gene of the invention. The gene described, when expressed, codes for a polypeptide, L<sub>1/4</sub>H<sub>423</sub>/A (SEQ ID NO: 10), which contains an additional four amino acids between amino acids 448 and 449 of LH<sub>423</sub>/A at a position equivalent to the amino terminus of the

heavy chain of native BoNT/A.

A variant of the gene has been expressed,  $L_{FXa/3}H_{423}/A$  (SEQ ID NO: 12), in which a specific proteolytic cleavage site was incorporated at the carboxy-terminal end of the light chain domain, specifically after residue 448 of  $L_{14}H_{423}/A$ . The cleavage site incorporated was for Factor Xa protease and was coded for by modification of SEQ ID NO: 1. It will be apparent to one skilled in the art that a cleavage site for another specified protease could be similarly incorporated, and that any gene sequence coding for the required cleavage site could be employed. Modification of the gene sequence in this manner to code for a defined protease site could be performed on any gene of the invention.

Variants of  $L_{FXa/3}H_{423}/A$  have been constructed in which a third domain is present at the carboxy-terminal end of the polypeptide which incorporates a specific binding activity into the polypeptide.

Specific examples described are:

(1)  $L_{FXa/3}H_{423}/A$ -IGF-1 (SEQ ID NO: 14) , in which the carboxy-terminal domain has a sequence equivalent to that of insulin-like growth factor-1 (IGF-1) and is able to bind to the insulin-like growth factor receptor with high affinity;

(2)  $L_{FXa/3}H_{423}/A$ -CtxA14 (SEQ ID NO: 16) , in which the carboxy-terminal domain has a sequence equivalent to that of the 14 amino acids from the carboxy-terminus of the A-subunit of cholera toxin (CtxA) and is thereby able to interact with the cholera toxin B-subunit pentamer; and

(3)  $L_{FXa/3}H_{423}/A$ -ZZ (SEQ ID NO: 18) , in which the carboxy-terminal domain is a tandem repeating synthetic IgG binding domain. This variant also exemplifies another modification applicable to the current invention, namely the inclusion in the gene of a sequence coding for a protease cleavage site located between the end

~~of the clostridial heavy chain sequence and the sequence coding for the binding~~

ligand. Specifically in this example a sequence is inserted at nucleotides 2650 to 2666 coding for a genenase cleavage site. Expression of this gene produces a polypeptide which has the desired protease sensitivity at the interface between the domain providing  $H_N$  function and the binding domain. Such a modification enables selective removal of the C-terminal binding domain by treatment of the polypeptide with the relevant protease.

It will be apparent that any one of a number of such binding domains could be incorporated into the polypeptide sequences of this invention and that the above examples are merely to exemplify the concept. Similarly, such binding domains can be incorporated into any of the polypeptide sequences that are the basis of this invention. Further, it should be noted that such binding domains could be incorporated at any appropriate location within the polypeptide molecules of the invention.

Further embodiments of the invention are thus illustrated by a DNA of the invention further comprising a desired restriction endonuclease site at a desired location and by a polypeptide of the invention further comprising a desired protease cleavage site at a desired location.

The restriction endonuclease site may be introduced so as to facilitate further manipulation of the DNA in manufacture of an expression vector for expressing a polypeptide of the invention; it may be introduced as a consequence of a previous step in manufacture of the DNA; it may be introduced by way of modification by insertion, substitution or deletion of a known sequence. The consequence of modification of the DNA may be that the amino acid sequence is unchanged, or may be that the amino acid sequence is changed, for example resulting in introduction of a desired protease cleavage site, either way the polypeptide retains its first and second domains having the properties required by the invention.

Figure 10 is a diagrammatic representation of an expression product exemplifying features described in this example. Specifically, it illustrates a single polypeptide-

incorporating a domain equivalent to the light chain of botulinum neurotoxin type A and a domain equivalent to the H<sub>N</sub> domain of the heavy chain of botulinum neurotoxin type A with a N-terminal extension providing an affinity purification domain, namely GST, and a C-terminal extension providing a ligand binding domain, namely an IgG binding domain. The domains of the polypeptide are spatially separated by specific protease cleavage sites enabling selective enzymatic separation of domains as exemplified in the Figure. This concept is more specifically depicted in Figure 11 where the various protease sensitivities are defined for the purpose of example.

#### Assay of product activity

The LC of botulinum neurotoxin type A exerts a zinc-dependent endopeptidase activity on the synaptic vesicle associated protein SNAP-25 which it cleaves in a specific manner at a single peptide bond. The <sub>2</sub>LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y) (SEQ ID NO: 6) cleaves a synthetic SNAP-25 substrate *in vitro* under the same conditions as the native toxin (Figure 3). Thus, the modification of the polypeptide sequence of <sub>2</sub>LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y) relative to the native sequence and within the minimal functional LC domains does not prevent the functional activity of the LC domains.

This activity is dependent on proteolytic modification of the recombinant GST-<sub>2</sub>LH<sub>423</sub>/A (Q<sub>2</sub>E,N<sub>26</sub>K,A<sub>27</sub>Y) to convert the single chain polypeptide product to a disulphide linked dichain species. This is currently done using the proteolytic enzyme trypsin. The recombinant product (100-600 µg/ml) is incubated at 37°C for 10-50 minutes with trypsin (10 µg/ml) in a solution containing 140 mM NaCl, 2.7 mM KCl, 10 mM Na<sub>2</sub>HPO<sub>4</sub>, 1.8 mM KH<sub>2</sub>PO<sub>4</sub>, pH 7.3. The reaction is terminated by addition of a 100-fold molar excess of trypsin inhibitor. The activation by trypsin generates a disulphide linked dichain species as determined by polyacrylamide gel electrophoresis and immunoblotting analysis using polyclonal anti-botulinum neurotoxin type A antiserum.

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<sub>2</sub>LH<sub>423</sub>/A is more stable in the presence of trypsin and more active in the *in vitro*



peptide cleavage assay than is  $_{23}\text{LH}_{423}/\text{A}$ . Both variants, however, are fully functional in the *in vitro* peptide cleavage assay. This demonstrates that the r combinant molecule will tolerate N-terminal amino acid extensions and this may be expanded to other chemical or organic moieties as would be obvious to those skilled in the art.

## Example 2

As a further exemplification of this invention a number of gene sequences have been assembled coding for polypeptides corresponding to the entire light-chain and varying numbers of residues from the amino terminal end of the heavy chain of botulinum neurotoxin type B. In this exemplification of the disclosure the gene sequences assembled were obtained from a combination of chromosomal and polymerase-chain-reaction generated DNA, and therefore have the nucleotide sequence of the equivalent regions of the natural genes, thus exemplifying the principle that the substance of this disclosure can be based upon natural as well as a synthetic gene sequences.

The gene sequences relating to this example were all assembled and expressed using methodologies as detailed in Sambrook J, Fritsch E F & Maniatis T (1989) Molecular Cloning: A Laboratory Manual (2nd Edition), Ford N, Nolan C, Ferguson M & Ockler M (eds), Cold Spring Harbor Laboratory Press, New York, and known to those skilled in the art.

A gene has been assembled coding for a polypeptide of 1171 amino acids corresponding to the entire light-chain (443 amino acids) and 728 residues from the amino terminus of the heavy chain of neurotoxin type B. Expression of this gene produces a polypeptide,  $\text{LH}_{728}/\text{B}$  (SEQ ID NO: 20), which lacks the specific neuronal binding activity of full length BoNT/B.

A gene has also been assembled coding for a variant polypeptide,  $\text{LH}_{417}/\text{B}$  (SEQ ID NO: 22), which possesses an amino acid sequence at its carboxy terminus

equivalent by amino acid homology to that at the carboxy-terminus of the heavy chain fragment in native LH<sub>N</sub>/A .

A gene has also been assembled coding for a variant polypeptide, LH<sub>107</sub>/B (SEQ ID NO: 24) , which expresses at its carboxy-terminus a short sequence from the amino terminus of the heavy chain of BoNT/B sufficient to maintain solubility of the expressed polypeptide.

### Construct Variants

A variant of the coding sequence for the first 274 bases of the gene shown in SEQ ID NO: 21 has been produced which whilst being a non-native nucleotide sequence still codes for the native polypeptide.

Two double stranded, a 268 base pair and a 951 base pair, gene sequences have been created using an overlapping primer PCR strategy. The nucleotide bias of these sequences was designed to have an *E.coli* codon usage bias.

For the first sequence, six oligonucleotides representing the first (5') 268 nucleotides of the native sequence for botulinum toxin type B were synthesised. For the second sequence 23 oligonucleotides representing internal sequence nucleotides 691-1641 of the native sequence for botulinum toxin type B were synthesised. The oligonucleotides ranged from 57-73 nucleotides in length. Overlapping regions, 17-20 nucleotides, were designed to give melting temperatures in the range 52-56°C. In addition, terminal restriction endonuclease sites of the synthetic products were constructed to facilitate insertion of these products into the exact corresponding region of the native sequence. The 268 bp 5' synthetic sequence has been incorporated into the gene shown in SEQ ID NO: 21 in place of the original first 268 bases (and is shown in SEQ ID NO: 27).

Similarly the sequence could be inserted into other genes of the examples.

----- Another variant sequence equivalent to nucleotides 691 to 1641 of SEQ ID NO: 21 -----

, and employing non-native codon usage whilst coding for a native polypeptide sequence, has been constructed using the internal synthetic sequence. This sequence (SEQ ID NO: 28) can be incorporated, alone or in combination with other variant sequences, in place of the equivalent coding sequence in any of the genes of the example.

### Example 3

An exemplification of the utility of this invention is as a non-toxic and effective immunogen. The non-toxic nature of the recombinant, single chain material was demonstrated by intraperitoneal administration in mice of GST-<sub>2</sub>LH<sub>423</sub>/A. The polypeptide was prepared and purified as described above. The amount of immunoreactive material in the final preparation was determined by enzyme linked immunosorbent assay (ELISA) using a monoclonal antibody (BA11) reactive against a conformation dependent epitope on the native LH<sub>N</sub>/A. The recombinant material was serially diluted in phosphate buffered saline (PBS; NaCl 8 g/l, KCl 0.2 g/l, Na<sub>2</sub>HPO<sub>4</sub> 1.15 g/l, KH<sub>2</sub>PO<sub>4</sub> 0.2 g/l, pH 7.4) and 0.5 ml volumes injected into 3 groups of 4 mice such that each group of mice received 10, 5 and 1 micrograms of material respectively. Mice were observed for 4 days and no deaths were seen.

For immunisation, 20 µg of GST-<sub>2</sub>LH<sub>423</sub>/A in a 1.0 ml volume of water-in-oil emulsion (1:1 vol:vol) using Freund's complete (primary injections only) or Freund's incomplete adjuvant was administered into guinea pigs via two sub-cutaneous dorsal injections. Three injections at 10 day intervals were given (day 1, day 10 and day 20) and antiserum collected on day 30. The antisera were shown by ELISA to be immunoreactive against native botulinum neurotoxin type A and to its derivative LH<sub>N</sub>/A. Antisera which were botulinum neurotoxin reactive at a dilution of 1:2000 were used for evaluation of neutralising efficacy in mice. For neutralisation assays 0.1 ml of antiserum was diluted into 2.5 ml of gelatine phosphate buffer (GPB; Na<sub>2</sub>HPO<sub>4</sub> anhydrous 10 g/l, gelatin (Difco) 2 g/l, pH 6.5-6.6) containing a dilution range from 0.5 µg (5X10<sup>-6</sup> g) to 5 picograms (5X10<sup>-12</sup> g). Aliquots of 0.5 ml were injected into mice intraperitoneally and deaths recorded

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over a 4 day period. The results are shown in Table 1 and Table 2. It can clearly be seen that 0.5 ml of 1:40 diluted anti- GST-<sub>2</sub>LH<sub>423</sub>/A antiserum can protect mice against intraperitoneal challenge with botulinum neurotoxin in the range 5 pg - 50 ng (1 - 10,000 mouse LD50; 1 mouse LD50 = 5 pg).

**TABLE 1.** Neutralisation of botulinum neurotoxin in mice by guinea pig anti-GST-LH<sub>423</sub>/A antiserum.

Survivors On Day	<u>Botulinum Toxin/mouse</u>						Control (no toxin)
	0.5 $\mu$ g	0.005 $\mu$ g	0.0005 $\mu$ g	0.5ng	0.005ng	5pg	
1	0	4	4	4	4	4	4
2	-	4	4	4	4	4	4
3	-	4	4	4	4	4	4
4	-	4	4	4	4	4	4

**TABLE 2.** Neutralisation of botulinum neurotoxin in mice by non-immune guinea pig antiserum.

Survivors On Day	<u>Botulinum Toxin/mouse</u>						Control (no toxin)
	0.5 $\mu$ g	0.005 $\mu$ g	0.0005 $\mu$ g	0.5ng	0.005ng	5pg	
1	0	0	0	0	0	2	4
2	-	-	-	-	-	0	4
3	-	-	-	-	-	-	4
4	-	-	-	-	-	-	4

#### Example 4

Expression of recombinant LH<sub>107</sub>/B in *E. coli*.

As an exemplification of the expression of a nucleic acid coding for a LH<sub>N</sub> of a clostridial neurotoxin of a serotype other than botulinum neurotoxin type A, the nucleic acid sequence (SEQ ID NO: 23) coding for the polypeptide LH<sub>107</sub>/B (SEQ ID

NO: 24) was inserted into the commercially available plasmid pET28a (Novogen, Madison, WI, USA). The nucleic acid was expressed in *E. coli* BL21 (DE3) (New England BioLabs, Beverley, MA, USA) as a fusion protein with a N-terminal T7 fusion peptide, under IPTG induction at 1 mM for 90 minutes at 37°C. Cultures were harvested and recombinant protein extracted as described previously for LH<sub>423</sub>/A.

Recombinant protein was recovered and purified from bacterial paste lysates by immunoaffinity adsorption to an immobilised anti-T7 peptide monoclonal antibody using a T7 tag purification kit (New England bioLabs, Beverley, MA, USA). Purified recombinant protein was analysed by gradient (4-20%) denaturing SDS-polyacrylamide gel electrophoresis (Novex, San Diego, CA, USA) and western blotting using polyclonal anti-botulinum neurotoxin type antiserum or anti-T7 antiserum. Western blotting reagents were from Novex, immunostained proteins were visualised using the Enhanced Chemi-Luminescence system (ECL) from Amersham. The expression of an anti-T7 antibody and anti-botulinum neurotoxin type B antiserum reactive recombinant product is demonstrated in Figure 13.

The recombinant product was soluble and retained that part of the light chain responsible for endopeptidase activity.

The invention thus provides recombinant polypeptides useful inter alia as immunogens, enzyme standards and components for synthesis of molecules as described in WO-A-94/21300.

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## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

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(F) POSTAL CODE (ZIP): SP4 0JG

(ii) TITLE OF INVENTION: Recombinant Toxin Fragments

(iii) NUMBER OF SEQUENCES: 28

## (iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

## (2) INFORMATION FOR SEQ ID NO: 1:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2616 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

## (ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION:1..2616

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

ATG CAG TTC GTG AAC AAG CAG TTC AAC TAT AAG GAC CCT GTA AAC GGT Met Gln Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly 1 5 10 15	48
GTT GAC ATT GCC TAC ATC AAA ATT CCA AAC GCC GGC CAG ATG CAG CCG Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro 20 25 30	96
GTG AAG GCT TTC AAG ATT CAT AAC AAA ATC TGG GTT ATT CCG GAA CGC Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg 35 40 45	144
GAT ACA TTT ACG AAC CCG GAA GAA GGA GAC TTG AAC CCG CCG CCG GAA Asp Thr Phe Thr Asn Pro Glu Gly Asp Leu Asn Pro Pro Pro Glu 50 55 60	192
GCA AAG CAG GTG CCA GTT TCA TAC TAC GAT TCA ACC TAT CTG AGC ACA Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr 65 70 75 80	240
GAC AAC GAG AAG GAT AAC TAC CTG AAG GGA GTG ACC AAA TTA TTC GAG Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu 85 90 95	288
CGT ATT TAT TCC ACT GAC CTG GGC CGT ATG CTG CTG ACC TCA ATC GTC Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val 100 105 110	336
CGC GGA ATC CCA TTT TGG GGT GGC AGT ACC ATT GAC ACG GAG TTG AAG Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys 115 120 125	384
GTT ATT GAC ACT AAC TGC ATT AAC GTG ATC CAA CCA GAC GGT AGC TAC Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr 130 135 140	432
AGA TCT GAA GAA CTT AAC CTC GTA ATC ATC GGG CCC TCC GCG GAC ATT Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile 145 150 155 160	480
ATC CAG TTT GAG TGC AAG AGC TTT GGC CAC GAA GTG TTG AAC CTG ACG Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr 165 170 175	528
CGT AAC GGT TAC GGC TCT ACT CAG TAC ATT CGT TTC AGC CCA GAC TTC Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Asp Phe 180 185 190	576
ACG TTC GGT TTC GAG GAG AGC CTG GAG GTT GAT ACC AAC CCG CTG TTG Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu 195 200 205	624
GGT GCA GGC AAG TTC GCA ACT GAT CCA GCG GTG ACC CTG GCA CAC GAG Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu 210 215 220	672
CTG ATC CAC GCC GGT CAT CGT CTG TAT GGC ATT GCG ATT AAC CCG AAC Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn 225 230 235 240	720



CGC	GTG	TTC	AAG	GTT	AAC	ACC	AAC	GCC	TAC	TAC	GAG	ATG	AGT	GGT	TTA	768
Arg	Val	Phe	Lys	Val	Asn	Thr	Asn	Ala	Tyr	Tyr	Glu	Met	Ser	Gly	Leu	
				245					250					255		
GAA	GTA	AGC	TTC	GAG	GAA	CTG	CGC	ACG	TTC	GGT	GGC	CAT	GAT	GCG	AAG	816
Glu	Val	Ser	Phe	Glu	Glu	Leu	Arg	Thr	Phe	Gly	Gly	His	Asp	Ala	Lys	
			260					265					270			
TTT	ATC	GAC	AGC	TTG	CAG	GAG	AAC	GAG	TTC	CGT	CTG	TAC	TAC	TAC	AAC	864
Phe	Ile	Asp	Ser	Leu	Gln	Glu	Asn	Glu	Phe	Arg	Leu	Tyr	Tyr	Tyr	Asn	
		275					280					285				
AAG	TTT	AAA	GAT	ATT	GCA	AGT	ACA	CTG	AAC	AAG	GCT	AAG	TCC	ATT	GTG	912
Lys	Phe	Lys	Asp	Ile	Ala	Ser	Thr	Leu	Asn	Lys	Ala	Lys	Ser	Ile	Val	
	290					295					300					
GGT	ACC	ACT	GCT	TCA	TTA	CAG	TAT	ATG	AAA	AAT	GTT	TTT	AAA	GAG	AAA	960
Gly	Thr	Thr	Ala	Ser	Leu	Gln	Tyr	Met	Lys	Asn	Val	Phe	Lys	Glu	Lys	
305					310					315					320	
TAT	CTC	CTA	TCT	GAA	GAT	ACA	TCT	GGA	AAA	TTT	TCG	GTA	GAT	AAA	TTA	1008
Tyr	Leu	Leu	Ser	Glu	Asp	Thr	Ser	Gly	Lys	Phe	Ser	Val	Asp	Lys	Leu	
				325					330					335		
AAA	TTT	GAT	AAG	TTA	TAC	AAA	ATG	TTA	ACA	GAG	ATT	TAC	ACA	GAG	GAT	1056
Lys	Phe	Asp	Lys	Leu	Tyr	Lys	Met	Leu	Thr	Glu	Ile	Tyr	Thr	Glu	Asp	
			340					345					350			
AAT	TTT	GTT	AAG	TTT	TTT	AAA	GTA	CTT	AAC	AGA	AAA	ACA	TAT	TTG	AAT	1104
Asn	Phe	Val	Lys	Phe	Phe	Lys	Val	Leu	Asn	Arg	Lys	Thr	Tyr	Leu	Asn	
		355					360					365				
TTT	GAT	AAA	GCC	GTA	TTT	AAG	ATA	AAT	ATA	GTA	CCT	AAG	GTA	AAT	TAC	1152
Phe	Asp	Lys	Ala	Val	Phe	Lys	Ile	Asn	Ile	Val	Pro	Lys	Val	Asn	Tyr	
	370					375					380					
ACA	ATA	TAT	GAT	GGA	TTT	AAT	TTA	AGA	AAT	ACA	AAT	TTA	GCA	GCA	AAC	1200
Thr	Ile	Tyr	Asp	Gly	Phe	Asn	Leu	Arg	Asn	Thr	Asn	Leu	Ala	Ala	Asn	
385					390					395					400	
TTT	AAT	GGT	CAA	AAT	ACA	GAA	ATT	AAT	AAT	ATG	AAT	TTT	ACT	AAA	CTA	1248
Phe	Asn	Gly	Gln	Asn	Thr	Glu	Ile	Asn	Asn	Met	Asn	Phe	Thr	Lys	Leu	
				405					410					415		
AAA	AAT	TTT	ACT	GGA	TTG	TTT	GAA	TTT	TAT	AAG	TTG	CTA	TGT	GTA	AGA	1296
Lys	Asn	Phe	Thr	Gly	Leu	Phe	Glu	Phe	Tyr	Lys	Leu	Leu	Cys	Val	Arg	
			420					425					430			
GGG	ATA	ATA	ACT	TCT	AAA	ACT	AAA	TCA	TTA	GAT	AAA	GGA	TAC	AAT	AAG	1344
Gly	Ile	Ile	Thr	Ser	Lys	Thr	Lys	Ser	Leu	Asp	Lys	Gly	Tyr	Asn	Lys	
	435						440					445				
GCA	TTA	AAT	GAT	TTA	TGT	ATC	AAA	GTT	AAT	AAT	TGG	GAC	TTG	TTT	TTT	1392
Ala	Leu	Asn	Asp	Leu	Cys	Ile	Lys	Val	Asn	Asn	Trp	Asp	Leu	Phe	Phe	
	450					455					460					
AGT	CCT	TCA	GAA	GAT	AAT	TTT	ACT	AAT	GAT	CTA	AAT	AAA	GGA	GAA	GAA	1440
Ser	Pro	Ser	Glu	Asp	Asn	Phe	Thr	Asn	Asp	Leu	Asn	Lys	Gly	Glu	Glu	
465					470				475						480	
ATT	ACA	TCT	GAT	ACT	AAT	ATA	GAA	GCA	GCA	GAA	GAA	AAT	ATT	AGT	TTA	1488
Ile	Thr	Ser	Asp	Thr	Asn	Ile	Glu	Ala	Ala	Glu	Glu	Asn	Ile	Ser	Leu	
				485				490						495		
GAT	TTA	ATA	CAA	CAA	TAT	TAT	TTA	ACC	TTT	AAT	TTT	GAT	AAT	GAA	CCT	1536
Asp	Leu	Ile	Gln	Gln	Tyr	Tyr	Leu	Thr	Phe	Asn	Phe	Asp	Asn	Glu	Pro	
			500					505						510		

GAA Glu	AAT Asn	ATT Ile	TCA Ser	ATA Ile	GAA Glu	AAT Asn	CTT Leu	TCA Ser	AGT Ser	GAC Asp	ATT Ile	ATA Ile	GGC Gly	CAA Gln	TTA Leu	1584
		515					520					525				
GAA Glu	CTT Leu	ATG Met	CCT Pro	AAT Asn	ATA Ile	GAA Glu	AGA Arg	TTT Phe	CCT Pro	AAT Asn	GGA Gly	AAA Lys	AAG Lys	TAT Tyr	GAG Glu	1632
	530					535					540					
TTA Leu	GAT Asp	AAA Lys	TAT Tyr	ACT Thr	ATG Met	TTC Phe	CAT His	TAT Tyr	CTT Leu	CGT Arg	GCT Ala	CAA Gln	GAA Glu	TTT Phe	GAA Glu	1680
	545				550					555					560	
CAT His	GGT Gly	AAA Lys	TCT Ser	AGG Arg	ATT Ile	GCT Ala	TTA Leu	ACA Thr	AAT Asn	TCT Ser	GTT Val	AAC Asn	GAA Glu	GCA Ala	TTA Leu	1728
				565					570					575		
TTA Leu	AAT Asn	CCT Pro	AGT Ser	CGT Arg	GTT Val	TAT Tyr	ACA Thr	TTT Phe	TTT Phe	TCT Ser	TCA Ser	GAC Asp	TAT Tyr	GTA Val	AAG Lys	1776
			580					585					590			
AAA Lys	GTT Val	AAT Asn	AAA Lys	GCT Ala	ACG Thr	GAG Glu	GCA Ala	GCT Ala	ATG Met	TTT Phe	TTA Leu	GGC Gly	TGG Trp	GTA Val	GAA Glu	1824
		595					600					605				
CAA Gln	TTA Leu	GTA Val	TAT Tyr	GAT Asp	TTT Phe	ACC Thr	GAT Asp	GAA Glu	ACT Thr	AGC Ser	GAA Glu	GTA Val	AGT Ser	ACT Thr	ACG Thr	1872
	610					615					620					
GAT Asp	AAA Lys	ATT Ile	GCG Ala	GAT Asp	ATA Ile	ACT Thr	ATA Ile	ATT Ile	ATT Ile	CCA Pro	TAT Tyr	ATA Ile	GGA Gly	CCT Pro	GCT Ala	1920
	625				630					635					640	
TTA Leu	AAT Asn	ATA Ile	GGT Gly	AAT Asn	ATG Met	TTA Leu	TAT Tyr	AAA Lys	GAT Asp	GAT Asp	TTT Phe	GTA Val	GGT Gly	GCT Ala	TTA Leu	1968
				645					650					655		
ATA Ile	TTT Phe	TCA Ser	GGA Gly	GCT Ala	GTT Val	ATT Ile	CTG Leu	TTA Leu	GAA Glu	TTT Phe	ATA Ile	CCA Pro	GAG Glu	ATT Ile	GCA Ala	2016
			660				665						670			
ATA Ile	CCT Pro	GTA Val	TTA Leu	GGT Gly	ACT Thr	TTT Phe	GCA Ala	CTT Leu	GTA Val	TCA Ser	TAT Tyr	ATT Ile	GCG Ala	AAT Asn	AAG Lys	2064
		675					680					685				
GTT Val	CTA Leu	ACC Thr	GTT Val	CAA Gln	ACA Thr	ATA Ile	GAT Asp	AAT Asn	GCT Ala	TTA Leu	AGT Ser	AAA Lys	AGA Arg	AAT Asn	GAA Glu	2112
	690					695					700					
AAA Lys	TGG Trp	GAT Asp	GAG Glu	GTC Val	TAT Tyr	AAA Lys	TAT Tyr	ATA Ile	GTA Val	ACA Thr	AAT Asn	TGG Trp	TTA Leu	GCA Ala	AAG Lys	2160
	705				710					715					720	
GTT Val	AAT Asn	ACA Thr	CAG Gln	ATT Ile	GAT Asp	CTA Leu	ATA Ile	AGA Arg	AAA Lys	AAA Lys	ATG Met	AAA Lys	GAA Glu	GCT Ala	TTA Leu	2208
				725					730					735		
GAA Glu	AAT Asn	CAA Gln	GCA Ala	GAA Glu	GCA Ala	ACA Thr	AAG Lys	GCT Ala	ATA Ile	ATA Ile	AAC Asn	TAT Tyr	CAG Gln	TAT Tyr	AAT Asn	2256
			740					745					750			
CAA Gln	TAT Tyr	ACT Thr	GAG Glu	GAA Glu	GAG Glu	AAA Lys	AAT Asn	AAT Asn	ATT Ile	AAT Asn	TTT Phe	AAT Asn	ATT Ile	GAT Asp	GAT Asp	2304
		755					760					765				
TTA Leu	AGT Ser	TCG Ser	AAA Lys	CTT Leu	AAT Asn	GAG Glu	TCT Ser	ATA Ile	AAT Asn	AAA Lys	GCT Ala	ATG Met	ATT Ile	AAT Asn	ATA Ile	2352
	770					775					780					

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AAT AAA TTT TTG AAT CAA TGC TCT GTT TCA TAT TTA ATG AAT TCT ATG	2400
Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met	
785 790 795 800	
ATC CCT TAT GGT GTT AAA CGG TTA GAA GAT TTT GAT GCT AGT CTT AAA	2448
Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys	
805 810 815	
GAT GCA TTA TTA AAG TAT ATA TAT GAT AAT AGA GGA ACT TTA ATT GGT	2496
Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly	
820 825 830	
CAA GTA GAT AGA TTA AAA GAT AAA GTT AAT AAT ACA CTT AGT ACA GAT	2544
Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp	
835 840 845	
ATA CCT TTT CAG CTT TCC AAA TAC GTA GAT AAT CAA AGA TTA TTA TCT	2592
Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser	
850 855 860	
ACA TTT ACT GAA TAT ATT AAG TAA	2616
Thr Phe Thr Glu Tyr Ile Lys *	
865 870	

## (2) INFORMATION FOR SEQ ID NO: 2:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 872 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Met	Gln	Phe	Val	Asn	Lys	Gln	Phe	Asn	Tyr	Lys	Asp	Pro	Val	Asn	Gly
1				5					10					15	
Val	Asp	Ile	Ala	Tyr	Ile	Lys	Ile	Pro	Asn	Ala	Gly	Gln	Met	Gln	Pro
			20					25					30		
Val	Lys	Ala	Phe	Lys	Ile	His	Asn	Lys	Ile	Trp	Val	Ile	Pro	Glu	Arg
		35					40					45			
Asp	Thr	Phe	Thr	Asn	Pro	Glu	Glu	Gly	Asp	Leu	Asn	Pro	Pro	Pro	Glu
	50					55					60				
Ala	Lys	Gln	Val	Pro	Val	Ser	Tyr	Tyr	Asp	Ser	Thr	Tyr	Leu	Ser	Thr
65					70				75					80	
Asp	Asn	Glu	Lys	Asp	Asn	Tyr	Leu	Lys	Gly	Val	Thr	Lys	Leu	Phe	Glu
			85						90					95	
Arg	Ile	Tyr	Ser	Thr	Asp	Leu	Gly	Arg	Met	Leu	Leu	Thr	Ser	Ile	Val
			100					105					110		
Arg	Gly	Ile	Pro	Phe	Trp	Gly	Gly	Ser	Thr	Ile	Asp	Thr	Glu	Leu	Lys
	115					120					125				
Val	Ile	Asp	Thr	Asn	Cys	Ile	Asn	Val	Ile	Gln	Pro	Asp	Gly	Ser	Tyr
	130				135						140				
Arg	Ser	Glu	Glu	Leu	Asn	Leu	Val	Ile	Ile	Gly	Pro	Ser	Ala	Asp	Ile
145					150					155					160
Ile	Gln	Phe	Glu	Cys	Lys	Ser	Phe	Gly	His	Glu	Val	Leu	Asn	Leu	Thr
				165					170					175	

Arg	Asn	Gly	Tyr	Gly	Ser	Thr	Gln	Tyr	Ile	Arg	Phe	Ser	Pro	Asp	Phe
			180					185					190		
Thr	Phe	Gly	Phe	Glu	Glu	Ser	Leu	Glu	Val	Asp	Thr	Asn	Pro	Leu	Leu
		195					200					205			
Gly	Ala	Gly	Lys	Phe	Ala	Thr	Asp	Pro	Ala	Val	Thr	Leu	Ala	His	Glu
	210					215					220				
Leu	Ile	His	Ala	Gly	His	Arg	Leu	Tyr	Gly	Ile	Ala	Ile	Asn	Pro	Asn
225					230					235					240
Arg	Val	Phe	Lys	Val	Asn	Thr	Asn	Ala	Tyr	Tyr	Glu	Met	Ser	Gly	Leu
				245					250					255	
Glu	Val	Ser	Phe	Glu	Glu	Leu	Arg	Thr	Phe	Gly	Gly	His	Asp	Ala	Lys
			260					265					270		
Phe	Ile	Asp	Ser	Leu	Gln	Glu	Asn	Glu	Phe	Arg	Leu	Tyr	Tyr	Tyr	Asn
		275					280					285			
Lys	Phe	Lys	Asp	Ile	Ala	Ser	Thr	Leu	Asn	Lys	Ala	Lys	Ser	Ile	Val
	290					295					300				
Gly	Thr	Thr	Ala	Ser	Leu	Gln	Tyr	Met	Lys	Asn	Val	Phe	Lys	Glu	Lys
305					310					315					320
Tyr	Leu	Leu	Ser	Glu	Asp	Thr	Ser	Gly	Lys	Phe	Ser	Val	Asp	Lys	Leu
			325					330					335		
Lys	Phe	Asp	Lys	Leu	Tyr	Lys	Met	Leu	Thr	Glu	Ile	Tyr	Thr	Glu	Asp
			340					345					350		
Asn	Phe	Val	Lys	Phe	Phe	Lys	Val	Leu	Asn	Arg	Lys	Thr	Tyr	Leu	Asn
		355					360					365			
Phe	Asp	Lys	Ala	Val	Phe	Lys	Ile	Asn	Ile	Val	Pro	Lys	Val	Asn	Tyr
	370					375					380				
Thr	Ile	Tyr	Asp	Gly	Phe	Asn	Leu	Arg	Asn	Thr	Asn	Leu	Ala	Ala	Asn
385					390					395					400
Phe	Asn	Gly	Gln	Asn	Thr	Glu	Ile	Asn	Asn	Met	Asn	Phe	Thr	Lys	Leu
			405					410						415	
Lys	Asn	Phe	Thr	Gly	Leu	Phe	Glu	Phe	Tyr	Lys	Leu	Leu	Cys	Val	Arg
			420					425					430		
Gly	Ile	Ile	Thr	Ser	Lys	Thr	Lys	Ser	Leu	Asp	Lys	Gly	Tyr	Asn	Lys
		435					440					445			
Ala	Leu	Asn	Asp	Leu	Cys	Ile	Lys	Val	Asn	Asn	Trp	Asp	Leu	Phe	Phe
	450					455					460				
Ser	Pro	Ser	Glu	Asp	Asn	Phe	Thr	Asn	Asp	Leu	Asn	Lys	Gly	Glu	Glu
465					470					475					480
Ile	Thr	Ser	Asp	Thr	Asn	Ile	Glu	Ala	Ala	Glu	Glu	Asn	Ile	Ser	Leu
				485				490						495	
Asp	Leu	Ile	Gln	Gln	Tyr	Tyr	Leu	Thr	Phe	Asn	Phe	Asp	Asn	Glu	Pro
			500					505					510		
Glu	Asn	Ile	Ser	Ile	Glu	Asn	Leu	Ser	Ser	Asp	Ile	Ile	Gly	Gln	Leu
		515					520					525			

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Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu  
 530 535 540  
 Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu  
 545 550 555 560  
 His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu  
 565 570 575  
 Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys  
 580 585 590  
 Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu  
 595 600 605  
 Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr  
 610 615 620  
 Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala  
 625 630 635 640  
 Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu  
 645 650 655  
 Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala  
 660 665 670  
 Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys  
 675 680 685  
 Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu  
 690 695 700  
 Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys  
 705 710 715 720  
 Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu  
 725 730 735  
 Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn  
 740 745 750  
 Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp  
 755 760 765  
 Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile  
 770 775 780  
 Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met  
 785 790 795 800  
 Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys  
 805 810 815  
 Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly  
 820 825 830  
 Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp  
 835 840 845  
 Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser  
 850 855 860  
 Thr Phe Thr Glu Tyr Ile Lys \*  
 865 870

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2685 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (ix) FEATURE:

- (A) NAME/KEY: CDS  
 (B) LOCATION: 1..2685

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GGA TCC CCA GGA ATT CAT ATG ACG TCG ACG CGT CTG CAG AAG CTT CTA	48
Gly Ser Pro Gly Ile His Met Thr Ser Thr Arg Leu Gln Lys Leu Leu	
1 5 10 15	
GAA TTC GAG CTC CCG GGT ACC ATG GAG TTC GTG AAC AAG CAG TTC AAC	96
Glu Phe Glu Leu Pro Gly Thr Met Glu Phe Val Asn Lys Gln Phe Asn	
20 25 30	
TAT AAG GAC CCT GTA AAC GGT GTT GAC ATT GCC TAC ATC AAA ATT CCA	144
Tyr Lys Asp Pro Val Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro	
35 40 45	
AAG TAC GGC CAG ATG CAG CCG GTG AAG GCT TTC AAG ATT CAT AAC AAA	192
Lys Tyr Gly Gln Met Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys	
50 55 60	
ATC TGG GTT ATT CCG GAA CGC GAT ACA TTT ACG AAC CCG GAA GAA GGA	240
Ile Trp Val Ile Pro Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly	
65 70 75 80	
GAC TTG AAC CCG CCG CCG GAA GCA AAG CAG GTG CCA GTT TCA TAC TAC	288
Asp Leu Asn Pro Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr	
85 90 95	
GAT TCA ACC TAT CTG AGC ACA GAC AAC GAG AAG GAT AAC TAC CTG AAG	336
Asp Ser Thr Tyr Leu Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys	
100 105 110	
GGA GTG ACC AAA TTA TTC GAG CGT ATT TAT TCC ACT GAC CTG GGC CGT	384
Gly Val Thr Lys Leu Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg	
115 120 125	
ATG CTG CTG ACC TCA ATC GTC CGC GGA ATC CCA TTT TGG GGT GGC AGT	432
Met Leu Leu Thr Ser Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser	
130 135 140	
ACC ATT GAC ACG GAG TTG AAG GTT ATT GAC ACT AAC TGC ATT AAC GTG	480
Thr Ile Asp Thr Glu Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val	
145 150 155 160	
ATC CAA CCA GAC GGT AGC TAC AGA TCT GAA GAA CTT AAC CTC GTA ATC	528
Ile Gln Pro Asp Gly Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile	
165 170 175	
ATC GGG CCC TCC GCG GAC ATT ATC CAG TTT GAG TGC AAG AGC TTT GGC	576
Ile Gly Pro Ser Ala Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly	
180 185 190	
CAC GAA GTG TTG AAC CTG ACG CGT AAC GGT TAC GGC TCT ACT CAG TAC	624
His Glu Val Leu Asn Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr	
195 200 205	

ATT CGT TTC AGC CCA GAC TTC ACG TTC GGT TTC GAG GAG AGC CTG GAG Ile Arg Phe Ser Pro Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu 210 215 220	672
GTT GAT ACC AAC CCG CTG TTG GGT GCA GGC AAG TTC GCA ACT GAT CCA Val Asp Thr Asn Pro Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro 225 230 235 240	720
GCG GTG ACC CTG GCA CAC GAG CTG ATC CAC GCC GGT CAT CGT CTG TAT Ala Val Thr Leu Ala His Glu Leu Ile His Ala Gly His Arg Leu Tyr 245 250 255	768
GGC ATT GCG ATT AAC CCG AAC CGC GTG TTC AAG GTT AAC ACC AAC GCC Gly Ile Ala Ile Asn Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala 260 265 270	816
TAC TAC GAG ATG AGT GGT TTA GAA GTA AGC TTC GAG GAA CTG CGC ACG Tyr Tyr Glu Met Ser Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr 275 280 285	864
TTC GGT GGC CAT GAT GCG AAG TTT ATC GAC AGC TTG CAG GAG AAC GAG Phe Gly Gly His Asp Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu 290 295 300	912
TTC CGT CTG TAC TAC TAC AAC AAG TTT AAA GAT ATT GCA AGT ACA CTG Phe Arg Leu Tyr Tyr Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu 305 310 315 320	960
AAC AAG GCT AAG TCC ATT GTG GGT ACC ACT GCT TCA TTA CAG TAT ATG Asn Lys Ala Lys Ser Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met 325 330 335	1008
AAA AAT GTT TTT AAA GAG AAA TAT CTC CTA TCT GAA GAT ACA TCT GGA Lys Asn Val Phe Lys Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly 340 345 350	1056
AAA TTT TCG GTA GAT AAA TTA AAA TTT GAT AAG TTA TAC AAA ATG TTA Lys Phe Ser Val Asp Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu 355 360 365	1104
ACA GAG ATT TAC ACA GAG GAT AAT TTT GTT AAG TTT TTT AAA GTA CTT Thr Glu Ile Tyr Thr Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu 370 375 380	1152
AAC AGA AAA ACA TAT TTG AAT TTT GAT AAA GCC GTA TTT AAG ATA AAT Asn Arg Lys Thr Tyr Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn 385 390 395 400	1200
ATA GTA CCT AAG GTA AAT TAC ACA ATA TAT GAT GGA TTT AAT TTA AGA Ile Val Pro Lys Val Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg 405 410 415	1248
AAT ACA AAT TTA GCA GCA AAC TTT AAT GGT CAA AAT ACA GAA ATT AAT Asn Thr Asn Leu Ala Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn 420 425 430	1296
AAT ATG AAT TTT ACT AAA CTA AAA AAT TTT ACT GGA TTG TTT GAA TTT Asn Met Asn Phe Thr Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe 435 440 445	1344
TAT AAG TTG CTA TGT GTA AGA GGG ATA ATA ACT TCT AAA ACT AAA TCA Tyr Lys Leu Leu Cys Val Arg Gly Ile Ile Thr Ser Lys Thr Lys Ser 450 455 460	1392
TTA GAT AAA GGA TAC AAT AAG GCA TTA AAT GAT TTA TGT ATC AAA GTT Leu Asp Lys Gly Tyr Asn Lys Ala Leu Asn Asp Leu Cys Ile Lys Val 465 470 475 480	1440

AAT	AAT	TGG	GAC	TTG	TTT	TTT	AGT	CCT	TCA	GAA	GAT	AAT	TTT	ACT	AAT	1488
Asn	Asn	Trp	Asp	Leu	Phe	Phe	Ser	Pro	Ser	Glu	Asp	Asn	Phe	Thr	Asn	
				485					490					495		
GAT	CTA	AAT	AAA	GGA	GAA	GAA	ATT	ACA	TCT	GAT	ACT	AAT	ATA	GAA	GCA	1536
Asp	Leu	Asn	Lys	Gly	Glu	Glu	Ile	Thr	Ser	Asp	Thr	Asn	Ile	Glu	Ala	
			500					505					510			
GCA	GAA	GAA	AAT	ATT	AGT	TTA	GAT	TTA	ATA	CAA	CAA	TAT	TAT	TTA	ACC	1584
Ala	Glu	Glu	Asn	Ile	Ser	Leu	Asp	Leu	Ile	Gln	Gln	Tyr	Tyr	Leu	Thr	
			515				520					525				
TTT	AAT	TTT	GAT	AAT	GAA	CCT	GAA	AAT	ATT	TCA	ATA	GAA	AAT	CTT	TCA	1632
Phe	Asn	Phe	Asp	Asn	Glu	Pro	Glu	Asn	Ile	Ser	Ile	Glu	Asn	Leu	Ser	
	530					535						540				
AGT	GAC	ATT	ATA	GGC	CAA	TTA	GAA	CTT	ATG	CCT	AAT	ATA	GAA	AGA	TTT	1680
Ser	Asp	Ile	Ile	Gly	Gln	Leu	Glu	Leu	Met	Pro	Asn	Ile	Glu	Arg	Phe	
					550					555					560	
CCT	AAT	GGA	AAA	AAG	TAT	GAG	TTA	GAT	AAA	TAT	ACT	ATG	TTC	CAT	TAT	1728
Pro	Asn	Gly	Lys	Lys	Tyr	Glu	Leu	Asp	Lys	Tyr	Thr	Met	Phe	His	Tyr	
				565					570					575		
CTT	CGT	GCT	CAA	GAA	TTT	GAA	CAT	GGT	AAA	TCT	AGG	ATT	GCT	TTA	ACA	1776
Leu	Arg	Ala	Gln	Glu	Phe	Glu	His	Gly	Lys	Ser	Arg	Ile	Ala	Leu	Thr	
			580					585					590			
AAT	TCT	GTT	AAC	GAA	GCA	TTA	TTA	AAT	CCT	AGT	CGT	GTT	TAT	ACA	TTT	1824
Asn	Ser	Val	Asn	Glu	Ala	Leu	Leu	Asn	Pro	Ser	Arg	Val	Tyr	Thr	Phe	
		595					600					605				
TTT	TCT	TCA	GAC	TAT	GTA	AAG	AAA	GTT	AAT	AAA	GCT	ACG	GAG	GCA	GCT	1872
Phe	Ser	Ser	Asp	Tyr	Val	Lys	Lys	Val	Asn	Lys	Ala	Thr	Glu	Ala	Ala	
	610					615					620					
ATG	TTT	TTA	GGC	TGG	GTA	GAA	CAA	TTA	GTA	TAT	GAT	TTT	ACC	GAT	GAA	1920
Met	Phe	Leu	Gly	Trp	Val	Glu	Gln	Leu	Val	Tyr	Asp	Phe	Thr	Asp	Glu	
					630					635					640	
ACT	AGC	GAA	GTA	AGT	ACT	ACG	GAT	AAA	ATT	GCG	GAT	ATA	ACT	ATA	ATT	1968
Thr	Ser	Glu	Val	Ser	Thr	Thr	Asp	Lys	Ile	Ala	Asp	Ile	Thr	Ile	Ile	
				645					650					655		
ATT	CCA	TAT	ATA	GGA	CCT	GCT	TTA	AAT	ATA	GGT	AAT	ATG	TTA	TAT	AAA	2016
Ile	Pro	Tyr	Ile	Gly	Pro	Ala	Leu	Asn	Ile	Gly	Asn	Met	Leu	Tyr	Lys	
			660					665					670			
GAT	GAT	TTT	GTA	GGT	GCT	TTA	ATA	TTT	TCA	GGA	GCT	GTT	ATT	CTG	TTA	2064
Asp	Asp	Phe	Val	Gly	Ala	Leu	Ile	Phe	Ser	Gly	Ala	Val	Ile	Leu	Leu	
		675					680					685				
GAA	TTT	ATA	CCA	GAG	ATT	GCA	ATA	CCT	GTA	TTA	GGT	ACT	TTT	GCA	CTT	2112
Glu	Phe	Ile	Pro	Glu	Ile	Ala	Ile	Pro	Val	Leu	Gly	Thr	Phe	Ala	Leu	
		690					695				700					
GTA	TCA	TAT	ATT	GCG	AAT	AAG	GTT	CTA	ACC	GTT	CAA	ACA	ATA	GAT	AAT	2160
Val	Ser	Tyr	Ile	Ala	Asn	Lys	Val	Leu	Thr	Val	Gln	Thr	Ile	Asp	Asn	
					710					715					720	
GCT	TTA	AGT	AAA	AGA	AAT	GAA	AAA	TGG	GAT	GAG	GTC	TAT	AAA	TAT	ATA	2208
Ala	Leu	Ser	Lys	Arg	Asn	Glu	Lys	Trp	Asp	Glu	Val	Tyr	Lys	Tyr	Ile	
				725					730					735		
GTA	ACA	AAT	TGG	TTA	GCA	AAG	GTT	AAT	ACA	CAG	ATT	GAT	CTA	ATA	AGA	2256
Val	Thr	Asn	Trp	Leu	Ala	Lys	Val	Asn	Thr	Gln	Ile	Asp	Leu	Ile	Arg	
			740					745					750			



AAA	AAA	ATG	AAA	GAA	GCT	TTA	GAA	AAT	CAA	GCA	GAA	GCA	ACA	AAG	GCT	2304
Lys	Lys	Met	Lys	Glu	Ala	Leu	Glu	Asn	Gln	Ala	Glu	Ala	Thr	Lys	Ala	
		755					760					765				
ATA	ATA	AAC	TAT	CAG	TAT	AAT	CAA	TAT	ACT	GAG	GAA	GAG	AAA	AAT	AAT	2352
Ile	Ile	Asn	Tyr	Gln	Tyr	Asn	Gln	Tyr	Thr	Glu	Glu	Glu	Lys	Asn	Asn	
		770				775					780					
ATT	AAT	TTT	AAT	ATT	GAT	GAT	TTA	AGT	TCG	AAA	CTT	AAT	GAG	TCT	ATA	2400
Ile	Asn	Phe	Asn	Ile	Asp	Asp	Leu	Ser	Ser	Lys	Leu	Asn	Glu	Ser	Ile	
					790					795					800	
AAT	AAA	GCT	ATG	ATT	AAT	ATA	AAT	AAA	TTT	TTG	AAT	CAA	TGC	TCT	GTT	2448
Asn	Lys	Ala	Met	Ile	Asn	Ile	Asn	Lys	Phe	Leu	Asn	Gln	Cys	Ser	Val	
				805					810					815		
TCA	TAT	TTA	ATG	AAT	TCT	ATG	ATC	CCT	TAT	GGT	GTT	AAA	CGG	TTA	GAA	2496
Ser	Tyr	Leu	Met	Asn	Ser	Met	Ile	Pro	Tyr	Gly	Val	Lys	Arg	Leu	Glu	
			820					825					830			
GAT	TTT	GAT	GCT	AGT	CTT	AAA	GAT	GCA	TTA	TTA	AAG	TAT	ATA	TAT	GAT	2544
Asp	Phe	Asp	Ala	Ser	Leu	Lys	Asp	Ala	Leu	Leu	Lys	Tyr	Ile	Tyr	Asp	
		835					840					845				
AAT	AGA	GGA	ACT	TTA	ATT	GGT	CAA	GTA	GAT	AGA	TTA	AAA	GAT	AAA	GTT	2592
Asn	Arg	Gly	Thr	Leu	Ile	Gly	Gln	Val	Asp	Arg	Leu	Lys	Asp	Lys	Val	
	850					855					860					
AAT	AAT	ACA	CTT	AGT	ACA	GAT	ATA	CCT	TTT	CAG	CTT	TCC	AAA	TAC	GTA	2640
Asn	Asn	Thr	Leu	Ser	Thr	Asp	Ile	Pro	Phe	Gln	Leu	Ser	Lys	Tyr	Val	
	865				870					875					880	
GAT	AAT	CAA	AGA	TTA	TTA	TCT	ACA	TTT	ACT	GAA	TAT	ATT	AAG	TAA		2685
Asp	Asn	Gln	Arg	Leu	Leu	Ser	Thr	Phe	Thr	Glu	Tyr	Ile	Lys	*		
			885						890				895			

## (2) INFORMATION FOR SEQ ID NO: 4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 895 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Gly Ser Pro Gly Ile His Met Thr Ser Thr Arg Leu Gln Lys Leu Leu  
 1 5 10 15

Glu Phe Glu Leu Pro Gly Thr Met Glu Phe Val Asn Lys Gln Phe Asn  
 20 25 30 35

Tyr Lys Asp Pro Val Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro  
 35 40 45

Lys Tyr Gly Gln Met Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys  
 50 55 60

Ile Trp Val Ile Pro Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly  
 65 70 75 80

Asp Leu Asn Pro Pro Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr  
 85 90 95

Asp Ser Thr Tyr Leu Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys  
 100 105 110

Gly	Val	Thr	Lys	Leu	Phe	Glu	Arg	Ile	Tyr	Ser	Thr	Asp	Leu	Gly	Arg		
	115						120					125					
Met	Leu	Leu	Thr	Ser	Ile	Val	Arg	Gly	Ile	Pro	Phe	Trp	Gly	Gly	Ser		
	130					135					140						
Thr	Ile	Asp	Thr	Glu	Leu	Lys	Val	Ile	Asp	Thr	Asn	Cys	Ile	Asn	Val		
	145				150					155					160		
Ile	Gln	Pro	Asp	Gly	Ser	Tyr	Arg	Ser	Glu	Glu	Leu	Asn	Leu	Val	Ile		
				165					170					175			
Ile	Gly	Pro	Ser	Ala	Asp	Ile	Ile	Gln	Phe	Glu	Cys	Lys	Ser	Phe	Gly		
			180					185					190				
His	Glu	Val	Leu	Asn	Leu	Thr	Arg	Asn	Gly	Tyr	Gly	Ser	Thr	Gln	Tyr		
	195						200					205					
Ile	Arg	Phe	Ser	Pro	Asp	Phe	Thr	Phe	Gly	Phe	Glu	Glu	Ser	Leu	Glu		
	210					215					220						
Val	Asp	Thr	Asn	Pro	Leu	Leu	Gly	Ala	Gly	Lys	Phe	Ala	Thr	Asp	Pro		
	225				230					235					240		
Ala	Val	Thr	Leu	Ala	His	Glu	Leu	Ile	His	Ala	Gly	His	Arg	Leu	Tyr		
				245					250					255			
Gly	Ile	Ala	Ile	Asn	Pro	Asn	Arg	Val	Phe	Lys	Val	Asn	Thr	Asn	Ala		
		260						265					270				
Tyr	Tyr	Glu	Met	Ser	Gly	Leu	Glu	Val	Ser	Phe	Glu	Glu	Leu	Arg	Thr		
		275				280						285					
Phe	Gly	Gly	His	Asp	Ala	Lys	Phe	Ile	Asp	Ser	Leu	Gln	Glu	Asn	Glu		
	290					295					300						
Phe	Arg	Leu	Tyr	Tyr	Tyr	Asn	Lys	Phe	Lys	Asp	Ile	Ala	Ser	Thr	Leu		
	305				310					315					320		
Asn	Lys	Ala	Lys	Ser	Ile	Val	Gly	Thr	Thr	Ala	Ser	Leu	Gln	Tyr	Met		
				325					330					335			
Lys	Asn	Val	Phe	Lys	Glu	Lys	Tyr	Leu	Leu	Ser	Glu	Asp	Thr	Ser	Gly		
		340						345					350				
Lys	Phe	Ser	Val	Asp	Lys	Leu	Lys	Phe	Asp	Lys	Leu	Tyr	Lys	Met	Leu		
		355					360					365					
Thr	Glu	Ile	Tyr	Thr	Glu	Asp	Asn	Phe	Val	Lys	Phe	Phe	Lys	Val	Leu		
	370				375						380						
Asn	Arg	Lys	Thr	Tyr	Leu	Asn	Phe	Asp	Lys	Ala	Val	Phe	Lys	Ile	Asn		
	385				390					395					400		
Ile	Val	Pro	Lys	Val	Asn	Tyr	Thr	Ile	Tyr	Asp	Gly	Phe	Asn	Leu	Arg		
				405					410					415			
Asn	Thr	Asn	Leu	Ala	Ala	Asn	Phe	Asn	Gly	Gln	Asn	Thr	Glu	Ile	Asn		
		420					425						430				
Asn	Met	Asn	Phe	Thr	Lys	Leu	Lys	Asn	Phe	Thr	Gly	Leu	Phe	Glu	Phe		
		435					440					445					
Tyr	Lys	Leu	Leu	Cys	Val	Arg	Gly	Ile	Ile	Thr	Ser	Lys	Thr	Lys	Ser		
	450					455					460						

Leu Asp Lys Gly Tyr Asn Lys Ala Leu Asn Asp Leu Cys Ile Lys Val  
 465 470 475 480  
 Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn  
 485 490 495  
 Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala  
 500 505 510  
 Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr  
 515 520 525  
 Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser  
 530 535 540  
 Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe  
 545 550 555 560  
 Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr  
 565 570 575  
 Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr  
 580 585 590  
 Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe  
 595 600 605  
 Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala  
 610 615 620  
 Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu  
 625 630 635 640  
 Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile  
 645 650 655  
 Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys  
 660 665 670  
 Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu  
 675 680 685  
 Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu  
 690 695 700  
 Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn  
 705 710 715 720  
 Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile  
 725 730 735  
 Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg  
 740 745 750  
 Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala  
 755 760 765  
 Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn  
 770 775 780  
 Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile  
 785 790 795 800  
 Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val  
 805 810 815

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 2622 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

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(ix) FEATURE:
      (A) NAME/KEY: CDS
      (B) LOCATION:1..2622
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GGA Gly 1	TCC Ser	ATG Met	GAG Glu	TTC Phe 5	GTG Val	AAC Asn	AAG Lys	CAG Gln	TTC Phe 10	AAC Asn	TAT Tyr	AAG Lys	GAC Asp	CCT Pro 15	GTA Val	48
AAC Asn	GGT Gly	GTT Val	GAC Asp 20	ATT Ile	GCC Ala	TAC Tyr	ATC Ile	AAA Lys 25	ATT Ile	CCA Pro	AAG Lys	TAC Tyr	GGC Gly 30	CAG Gln	ATG Met	96
CAG Gln	CCG Pro	GTG Val 35	AAG Lys	GCT Ala	TTC Phe	AAG Lys	ATT Ile 40	CAT His	AAC Asn	AAA Lys	ATC Ile	TGG Trp 45	GTT Val	ATT Ile	CCG Pro	144
GAA Glu 50	CGC Arg	GAT Asp	ACA Thr	TTT Phe	ACG Thr	AAC Asn 55	CCG Pro	GAA Glu	GAA Glu	GGA Gly	GAC Asp 60	TTG Leu	AAC Asn	CCG Pro	CCG Pro	192
CCG Pro 65	GAA Glu	GCA Ala	AAG Lys	CAG Gln	GTG Val 70	CCA Pro	GTT Val	TCA Ser	TAC Tyr	TAC Tyr 75	GAT Asp	TCA Ser	ACC Thr	TAT Tyr	CTG Leu 80	240
AGC Ser	ACA Thr	GAC Asp	AAC Asn	GAG Glu 85	AAG Lys	GAT Asp	AAC Asn	TAC Tyr	CTG Leu 90	AAG Lys	GGA Gly	GTG Val	ACC Thr	AAA Lys 95	TTA Leu	288
TTC Phe	GAG Glu	CGT Arg	ATT Ile 100	TAT Tyr	TCC Ser	ACT Thr	GAC Asp	CTG Leu 105	GGC Gly	CGT Arg	ATG Met	CTG Leu 110	CTG Leu	ACC Thr	TCA Ser	336
ATC Ile	GTC Val	CGC Arg 115	GGA Gly	ATC Ile	CCA Pro	TTT Phe	TGG Trp 120	GGT Gly	GGC Gly	AGT Ser	ACC Thr	ATT Ile 125	GAC Asp	ACG Thr	GAG Glu	384
TTG Leu 130	AAG Lys	GTT Val	ATT Ile	GAC Asp	ACT Thr	AAC Asn 135	TGC Cys	ATT Ile	AAC Asn	GTG Val	ATC Ile	CAA Gln	CCA Pro	GAC Asp	GGT Gly	432

AGC Ser 145	TAC Tyr	AGA Arg	TCT Ser	GAA Glu 150	GAA Glu 150	CTT Leu	AAC Asn	CTC Leu	GTA Val 155	ATC Ile 155	ATC Ile	GGG Gly	CCC Pro	TCC Ser	GCG Ala 160	480
GAC Asp	ATT Ile	ATC Ile	CAG Gln 165	TTT Phe 165	GAG Glu 165	TGC Cys	AAG Lys	AGC Ser	TTT Phe 170	GGC Gly 170	CAC His	GAA Glu	GTG Val	TTG Leu 175	AAC Asn 175	528
CTG Leu	ACG Thr	CGT Arg	AAC Asn 180	GGT Gly 180	TAC Tyr 180	GGC Gly 180	TCT Ser 185	ACT Thr 185	CAG Gln 185	TAC Tyr 185	ATT Ile 185	CGT Arg 190	TTC Phe 190	AGC Ser 190	CCA Pro 190	576
GAC Asp	TTC Phe 195	ACG Thr 195	TTC Phe 195	GGT Gly 195	TTC Phe 195	GAG Glu 200	GAG Glu 200	AGC Ser 200	CTG Leu 200	GAG Glu 200	GTT Val 205	GAT Asp 205	ACC Thr 205	AAC Asn 205	CCG Pro 205	624
CTG Leu 210	TTG Leu 210	GGT Gly 210	GCA Ala 210	GGC Gly 210	AAG Lys 215	TTC Phe 215	GCA Ala 215	ACT Thr 215	GAT Asp 215	CCA Pro 220	GCG Ala 220	GTG Val 220	ACC Thr 220	CTG Leu 220	GCA Ala 220	672
CAC His 225	GAG Glu 225	CTG Leu 225	ATC Ile 225	CAC His 230	GCC Ala 230	GGT Gly 230	CAT His 230	CGT Arg 230	CTG Leu 235	TAT Tyr 235	GGC Gly 235	ATT Ile 235	GCG Ala 235	ATT Ile 235	AAC Asn 240	720
CCG Pro	AAC Asn	CGC Arg	GTG Val 245	TTC Phe 245	AAG Lys 245	GTT Val 245	AAC Asn 250	ACC Thr 250	AAC Asn 250	GCC Ala 250	TAC Tyr 255	TAC Tyr 255	GAG Glu 255	ATG Met 255	AGT Ser 255	768
GGT Gly	TTA Leu	GAA Glu	GTA Val 260	AGC Ser 260	TTC Phe 260	GAG Glu 260	GAA Glu 265	CTG Leu 265	CGC Arg 265	ACG Thr 265	TTC Phe 265	GGT Gly 270	GGC Gly 270	CAT His 270	GAT Asp 270	816
GCG Ala	AAG Lys 275	TTT Phe 275	ATC Ile 275	GAC Asp 275	AGC Ser 280	TTG Leu 280	CAG Gln 280	GAG Glu 280	AAC Asn 285	GAG Glu 285	TTC Phe 285	CGT Arg 285	CTG Leu 285	TAC Tyr 285	TAC Tyr 285	864
TAC Tyr 290	AAC Asn 290	AAG Lys 290	TTT Phe 290	AAA Lys 295	GAT Asp 295	ATT Ile 295	GCA Ala 295	AGT Ser 295	ACA Thr 300	CTG Leu 300	AAC Asn 300	AAG Lys 300	GCT Ala 300	AAG Lys 300	TCC Ser 300	912
ATT Ile 305	GTG Val 305	GGT Gly 305	ACC Thr 310	ACT Thr 310	GCT Ala 310	TCA Ser 310	TTA Leu 310	CAG Gln 315	TAT Tyr 315	ATG Met 315	AAA Lys 315	AAT Asn 315	GTT Val 315	TTT Phe 320	AAA Lys 320	960
GAG Glu	AAA Lys	TAT Tyr	CTC Leu 325	CTA Leu 325	TCT Ser 325	GAA Glu 325	GAT Asp 330	ACA Thr 330	TCT Ser 330	GGA Gly 330	AAA Lys 335	TTT Phe 335	TCG Ser 335	GTA Val 335	GAT Asp 335	1008
AAA Lys	TTA Leu	AAA Lys	TTT Phe 340	GAT Asp 340	AAG Lys 340	TTA Leu 345	TAC Tyr 345	AAA Lys 345	ATG Met 350	TTA Leu 350	ACA Thr 350	GAG Glu 350	ATT Ile 350	TAC Tyr 350	ACA Thr 350	1056
GAG Glu	GAT Asp 355	AAT Asn 355	TTT Phe 355	GTT Val 355	AAG Lys 355	TTT Phe 360	TTT Phe 360	AAA Lys 360	GTA Val 360	CTT Leu 365	AAC Asn 365	AGA Arg 365	AAA Lys 365	ACA Thr 365	TAT Tyr 365	1104
TTG Leu 370	AAT Asn 370	TTT Phe 370	GAT Asp 370	AAA Lys 375	GCC Ala 375	GTA Val 375	TTT Phe 375	AAG Lys 375	ATA Ile 380	AAT Asn 380	ATA Ile 380	GTA Val 380	CCT Pro 380	AAG Lys 380	GTA Val 380	1152
AAT Asn 385	TAC Tyr	ACA Thr	ATA Ile	TAT Tyr	GAT Asp 390	GGA Gly 390	TTT Phe 390	AAT Asn 395	TTA Leu 395	AGA Arg 395	AAT Asn 395	ACA Thr 395	AAT Asn 395	TTA Leu 400	GCA Ala 400	1200
GCA Ala	AAC Asn	TTT Phe	AAT Asn	GGT Gly 405	CAA Gln 405	AAT Asn	ACA Thr	GAA Glu	ATT Ile	AAT Asn	AAT Asn	ATG Met	AAT Asn	TTT Phe	ACT Thr	1248

AAA CTA AAA AAT TTT ACT GGA TTG TTT GAA TTT TAT AAG TTG CTA TGT	1296
Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys	
420 425 430	
GTA AGA GGG ATA ATA ACT TCT AAA ACT AAA TCA TTA GAT AAA GGA TAC	1344
Val Arg Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Asp Lys Gly Tyr	
435 440 445	
AAT AAG GCA TTA AAT GAT TTA TGT ATC AAA GTT AAT AAT TGG GAC TTG	1392
Asn Lys Ala Leu Asn Asp Leu Cys Ile Lys Val Asn Asn Trp Asp Leu	
450 455 460	
TTT TTT AGT CCT TCA GAA GAT AAT TTT ACT AAT GAT CTA AAT AAA GGA	1440
Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly	
465 470 475 480	
GAA GAA ATT ACA TCT GAT ACT AAT ATA GAA GCA GCA GAA GAA AAT ATT	1488
Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile	
485 490 495	
AGT TTA GAT TTA ATA CAA CAA TAT TAT TTA ACC TTT AAT TTT GAT AAT	1536
Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn	
500 505 510	
GAA CCT GAA AAT ATT TCA ATA GAA AAT CTT TCA AGT GAC ATT ATA GGC	1584
Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly	
515 520 525	
CAA TTA GAA CTT ATG CCT AAT ATA GAA AGA TTT CCT AAT GGA AAA AAG	1632
Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys	
530 535 540	
TAT GAG TTA GAT AAA TAT ACT ATG TTC CAT TAT CTT CGT GCT CAA GAA	1680
Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu	
545 550 555 560	
TTT GAA CAT GGT AAA TCT AGG ATT GCT TTA ACA AAT TCT GTT AAC GAA	1728
Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu	
565 570 575	
GCA TTA TTA AAT CCT AGT CGT GTT TAT ACA TTT TTT TCT TCA GAC TAT	1776
Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr	
580 585 590	
GTA AAG AAA GTT AAT AAA GCT ACG GAG GCA GCT ATG TTT TTA GGC TGG	1824
Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp	
595 600 605	
GTA GAA CAA TTA GTA TAT GAT TTT ACC GAT GAA ACT AGC GAA GTA AGT	1872
Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser	
610 615 620	
ACT ACG GAT AAA ATT GCG GAT ATA ACT ATA ATT ATT CCA TAT ATA GGA	1920
Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly	
625 630 635 640	
CCT GCT TTA AAT ATA GGT AAT ATG TTA TAT AAA GAT GAT TTT GTA GGT	1968
Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly	
645 650 655	
GCT TTA ATA TTT TCA GGA GCT GTT ATT CTG TTA GAA TTT ATA CCA GAG	2016
Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu	
660 665 670	
ATT GCA ATA CCT GTA TTA GGT ACT TTT GCA CTT GTA TCA TAT ATT GCG	2064
Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala	
675 680 685	

- 45 -

AAT AAG GTT CTA ACC GTT CAA ACA ATA GAT AAT GCT TTA AGT AAA AGA Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg 690 695 700	2112
AAT GAA AAA TGG GAT GAG GTC TAT AAA TAT ATA GTA ACA AAT TGG TTA Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu 705 710 715 720	2160
GCA AAG GTT AAT ACA CAG ATT GAT CTA ATA AGA AAA AAA ATG AAA GAA Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu 725 730 735	2208
GCT TTA GAA AAT CAA GCA GAA GCA ACA AAG GCT ATA ATA AAC TAT CAG Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln 740 745 750	2256
TAT AAT CAA TAT ACT GAG GAA GAG AAA AAT AAT ATT AAT TTT AAT ATT Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile 755 760 765	2304
GAT GAT TTA AGT TCG AAA CTT AAT GAG TCT ATA AAT AAA GCT ATG ATT Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile 770 775 780	2352
AAT ATA AAT AAA TTT TTG AAT CAA TGC TCT GTT TCA TAT TTA ATG AAT Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn 785 790 795 800	2400
TCT ATG ATC CCT TAT GGT GTT AAA CGG TTA GAA GAT TTT GAT GCT AGT Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser 805 810 815	2448
CTT AAA GAT GCA TTA TTA AAG TAT ATA TAT GAT AAT AGA GGA ACT TTA Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu 820 825 830	2496
ATT GGT CAA GTA GAT AGA TTA AAA GAT AAA GTT AAT AAT ACA CTT AGT Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser 835 840 845	2544
ACA GAT ATA CCT TTT CAG CTT TCC AAA TAC GTA GAT AAT CAA AGA TTA Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu 850 855 860	2592
TTA TCT ACA TTT ACT GAA TAT ATT AAG TAA Leu Ser Thr Phe Thr Glu Tyr Ile Lys *	2622
865 870	

## (2) INFORMATION FOR SEQ ID NO: 6:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 874 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val  
1 5 10 15

Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Lys Tyr Gly Gln Met  
20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro  
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro  
 50 55 60  
 Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu  
 65 70 75 80  
 Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu  
 85 90 95  
 Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser  
 100 105 110  
 Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu  
 115 120 125  
 Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly  
 130 135 140  
 Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala  
 145 150 155 160  
 Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn  
 165 170 175  
 Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro  
 180 185 190  
 Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro  
 195 200 205  
 Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala  
 210 215 220  
 His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn  
 225 230 235 240  
 Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser  
 245 250 255  
 Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp  
 260 265 270  
 Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr  
 275 280 285  
 Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser  
 290 295 300  
 Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys  
 305 310 315 320  
 Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys-Phe Ser Val Asp  
 325 330 335  
 Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr  
 340 345 350  
 Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr  
 355 360 365  
 Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val  
 370 375 380  
 Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala  
 385 390 395 400



- 47 -

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr  
 405 410 415  
 Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys  
 420 425 430  
 Val Arg Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Asp Lys Gly Tyr  
 435 440 445  
 Asn Lys Ala Leu Asn Asp Leu Cys Ile Lys Val Asn Asn Trp Asp Leu  
 450 455 460  
 Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly  
 465 470 475 480  
 Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile  
 485 490 495  
 Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn  
 500 505 510  
 Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly  
 515 520 525  
 Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys  
 530 535 540  
 Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu  
 545 550 555 560  
 Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu  
 565 570 575  
 Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr  
 580 585 590  
 Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp  
 595 600 605  
 Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser  
 610 615 620  
 Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly  
 625 630 635 640  
 Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly  
 645 650 655  
 Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu  
 660 665 670  
 Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala  
 675 680 685  
 Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg  
 690 695 700  
 Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu  
 705 710 715 720  
 Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu  
 725 730 735  
 Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln  
 740 745 750

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 2613 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

(A) NAME/KEY: CDS  
(B) LOCATION:1..2613

ATG Met 1	CCA Pro	TTT Phe	GTT Val	AAT Asn 5	AAA Lys	CAA Gln	TTT Phe	AAT Asn	TAT Tyr 10	AAA Lys	GAT Asp	CCT Pro	GTA Val	AAT Asn 15	GGT Gly	48
GTT Val	GAT Asp	ATT Ile	GCT Ala 20	TAT Tyr	ATA Ile	AAA Lys	ATT Ile	CCA Pro 25	AAT Asn	GCA Ala	GGA Gly	CAA Gln	ATG Met 30	CAA Gln	CCA Pro	96
GTA Val	AAA Lys	GCT Ala 35	TTT Phe	AAA Lys	ATT Ile	CAT His	AAT Asn 40	AAA Lys	ATA Ile	TGG Trp	GTT Val	ATT Ile 45	CCA Pro	GAA Glu	AGA Arg	144
GAT Asp 50	ACA Thr	TTT Phe	ACA Thr	AAT Asn	CCT Pro	GAA Glu 55	GAA Glu	GGA Gly	GAT Asp	TTA Leu	AAT Asn 60	CCA Pro	CCA Pro	CCA Pro	GAA Glu	192
GCA Ala 65	AAA Lys	CAA Gln	GTT Val	CCA Pro	GTT Val 70	TCA Ser	TAT Tyr	TAT Tyr	GAT Asp	TCA Ser 75	ACA Thr	TAT Tyr	TTA Leu	AGT Ser	ACA Thr 80	240
GAT Asp	AAT Asn	GAA Glu	AAA Lys	GAT Asp 85	AAT Asn	TAT Tyr	TTA Leu	AAG Lys	GGA Gly 90	GTT Val	ACA Thr	AAA Lys	TTA Leu	TTT Phe 95	GAG Glu	288

AGA ATT TAT TCA ACT GAT CTT GGA AGA ATG TTG TTA ACA TCA ATA GTA	336
Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val	
100 105 110	
AGG GGA ATA CCA TTT TGG GGT GGA AGT ACA ATA GAT ACA GAA TTA AAA	384
Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys	
115 120 125	
GTT ATT GAT ACT AAT TGT ATT AAT GTG ATA CAA CCA GAT GGT AGT TAT	432
Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr	
130 135 140	
AGA TCA GAA GAA CTT AAT CTA GTA ATA ATA GGA CCC TCA GCT GAT ATT	480
Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile	
145 150 155 160	
ATA CAG TTT GAA TGT AAA AGC TTT GGA CAT GAA GTT TTG AAT CTT ACG	528
Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr	
165 170 175	
CGA AAT GGT TAT GGC TCT ACT CAA TAC ATT AGA TTT AGC CCA GAT TTT	576
Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe	
180 185 190	
ACA TTT GGT TTT GAG GAG TCA CTT GAA GTT GAT ACA AAT CCT CTT TTA	624
Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu	
195 200 205	
GGT GCA GGC AAA TTT GCT ACA GAT CCA GCA GTA ACA TTA GCA CAT GAA	672
Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu	
210 215 220	
CTT ATA CAT GCT GGA CAT AGA TTA TAT GGA ATA GCA ATT AAT CCA AAT	720
Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn	
225 230 235 240	
AGG GTT TTT AAA GTA AAT ACT AAT GCC TAT TAT GAA ATG AGT GGG TTA	768
Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu	
245 250 255	
GAA GTA AGC TTT GAG GAA CTT AGA ACA TTT GGG GGA CAT GAT GCA AAG	816
Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys	
260 265 270	
TTT ATA GAT AGT TTA CAG GAA AAC GAA TTT CGT CTA TAT TAT TAT AAT	864
Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn	
275 280 285	
AAG TTT AAA GAT ATA GCA AGT ACA CTT AAT AAA GCT AAA TCA ATA GTA	912
Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser Ile Val	
290 295 300	
GGT ACT ACT GCT TCA TTA CAG TAT ATG AAA AAT GTT TTT AAA GAG AAA	960
Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys Glu Lys	
305 310 315 320	
TAT CTC CTA TCT GAA GAT ACA TCT GGA AAA TTT TCG GTA GAT AAA TTA	1008
Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp Lys Leu	
325 330 335	
AAA TTT GAT AAG TTA TAC AAA ATG TTA ACA GAG ATT TAC ACA GAG GAT	1056
Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr Glu Asp	
340 345 350	
AAT TTT GTT AAG TTT TTT AAA GTA CTT AAC AGA AAA ACA TAT TTG AAT	1104
Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr Leu Asn	
355 360 365	

- 50 -

TTT GAT AAA GCC GTA TTT AAG ATA AAT ATA GTA CCT AAG GTA AAT TAC Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val Asn Tyr 370 375 380	1152
ACA ATA TAT GAT GGA TTT AAT TTA AGA AAT ACA AAT TTA GCA GCA AAC Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala Ala Asn 385 390 395 400	1200
TTT AAT GGT CAA AAT ACA GAA ATT AAT AAT ATG AAT TTT ACT AAA CTA Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr Lys Leu 405 410 415	1248
AAA AAT TTT ACT GGA TTG TTT GAA TTT TAT AAG TTG CTA TGT GTA AGA Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys Val Arg 420 425 430	1296
GGG ATA ATA ACT TCT AAA ACT AAA TCA TTA GAT AAA GGA TAC AAT AAG Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Asp Lys Gly Tyr Asn Lys 435 440 445	1344
GCA TTA AAT GAT TTA TGT ATC AAA GTT AAT AAT TGG GAC TTG TTT TTT Ala Leu Asn Asp Leu Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe 450 455 460	1392
AGT CCT TCA GAA GAT AAT TTT ACT AAT GAT CTA AAT AAA GGA GAA GAA Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu 465 470 475 480	1440
ATT ACA TCT GAT ACT AAT ATA GAA GCA GCA GAA GAA AAT ATT AGT TTA Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu 485 490 495	1488
GAT TTA ATA CAA CAA TAT TAT TTA ACC TTT AAT TTT GAT AAT GAA CCT Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro 500 505 510	1536
GAA AAT ATT TCA ATA GAA AAT CTT TCA AGT GAC ATT ATA GGC CAA TTA Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu 515 520 525	1584
GAA CTT ATG CCT AAT ATA GAA AGA TTT CCT AAT GGA AAA AAG TAT GAG Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu 530 535 540	1632
TTA GAT AAA TAT ACT ATG TTC CAT TAT CTT CGT GCT CAA GAA TTT GAA Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu 545 550 555 560	1680
CAT GGT AAA TCT AGG ATT GCT TTA ACA AAT TCT GTT AAC GAA GCA TTA His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu 565 570 575	1728
TTA AAT CCT AGT CGT GTT TAT ACA TTT TTT TCT TCA GAC TAT GTA AAG Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys 580 585 590	1776
AAA GTT AAT AAA GCT ACG GAG GCA GCT ATG TTT TTA GGC TGG GTA GAA Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu 595 600 605	1824
CAA TTA GTA TAT GAT TTT ACC GAT GAA ACT AGC GAA GTA AGT ACT ACG Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr 610 615 620	1872
GAT AAA ATT GCG GAT ATA ACT ATA ATT ATT CCA TAT ATA GGA CCT GCT Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala 625 630 635 640	1920

TTA AAT ATA GGT AAT ATG TTA TAT AAA GAT GAT TTT GTA GGT GCT TTA Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu 645 650 655	1968
ATA TTT TCA GGA GCT GTT ATT CTG TTA GAA TTT ATA CCA GAG ATT GCA Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala 660 665 670	2016
ATA CCT GTA TTA GGT ACT TTT GCA CTT GTA TCA TAT ATT GCG AAT AAG Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys 675 680 685	2064
GTT CTA ACC GTT CAA ACA ATA GAT AAT GCT TTA AGT AAA AGA AAT GAA Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu 690 695 700	2112
AAA TGG GAT GAG GTC TAT AAA TAT ATA GTA ACA AAT TGG TTA GCA AAG Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys 705 710 715 720	2160
GTT AAT ACA CAG ATT GAT CTA ATA AGA AAA AAA ATG AAA GAA GCT TTA Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu 725 730 735	2208
GAA AAT CAA GCA GAA GCA ACA AAG GCT ATA ATA AAC TAT CAG TAT AAT Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn 740 745 750	2256
CAA TAT ACT GAG GAA GAG AAA AAT AAT ATT AAT TTT AAT ATT GAT GAT Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp 755 760 765	2304
TTA AGT TCG AAA CTT AAT GAG TCT ATA AAT AAA GCT ATG ATT AAT ATA Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile 770 775 780	2352
AAT AAA TTT TTG AAT CAA TGC TCT GTT TCA TAT TTA ATG AAT TCT ATG Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met 785 790 795 800	2400
ATC CCT TAT GGT GTT AAA CGG TTA GAA GAT TTT GAT GCT AGT CTT AAA Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys 805 810 815	2448
GAT GCA TTA TTA AAG TAT ATA TAT GAT AAT AGA GGA ACT TTA ATT GGT Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly 820 825 830	2496
CAA GTA GAT AGA TTA AAA GAT AAA GTT AAT AAT ACA CTT AGT ACA GAT Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp 835 840 845	2544
ATA CCT TTT CAG CTT TCC AAA TAC GTA GAT AAT CAA AGA TTA TTA TCT Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser 850 855 860	2592
ACA TTT ACT GAA TAT ATT AAG Thr Phe Thr Glu Tyr Ile Lys 865 870	2613

## (2) INFORMATION FOR SEQ ID NO: 8:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 871 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

```

Met  Pro  Phe  Val  Asn  Lys  Gln  Phe  Asn  Tyr  Lys  Asp  Pro  Val  Asn  Gly
 1          5          10          15
Val  Asp  Ile  Ala  Tyr  Ile  Lys  Ile  Pro  Asn  Ala  Gly  Gln  Met  Gln  Pro
          20          25          30
Val  Lys  Ala  Phe  Lys  Ile  His  Asn  Lys  Ile  Trp  Val  Ile  Pro  Glu  Arg
          35          40          45
Asp  Thr  Phe  Thr  Asn  Pro  Glu  Glu  Gly  Asp  Leu  Asn  Pro  Pro  Pro  Glu
          50          55          60
Ala  Lys  Gln  Val  Pro  Val  Ser  Tyr  Tyr  Asp  Ser  Thr  Tyr  Leu  Ser  Thr
          65          70          75          80
Asp  Asn  Glu  Lys  Asp  Asn  Tyr  Leu  Lys  Gly  Val  Thr  Lys  Leu  Phe  Glu
          85          90          95
Arg  Ile  Tyr  Ser  Thr  Asp  Leu  Gly  Arg  Met  Leu  Leu  Thr  Ser  Ile  Val
          100          105          110
Arg  Gly  Ile  Pro  Phe  Trp  Gly  Gly  Ser  Thr  Ile  Asp  Thr  Glu  Leu  Lys
          115          120          125
Val  Ile  Asp  Thr  Asn  Cys  Ile  Asn  Val  Ile  Gln  Pro  Asp  Gly  Ser  Tyr
          130          135          140
Arg  Ser  Glu  Glu  Leu  Asn  Leu  Val  Ile  Ile  Gly  Pro  Ser  Ala  Asp  Ile
          145          150          155          160
Ile  Gln  Phe  Glu  Cys  Lys  Ser  Phe  Gly  His  Glu  Val  Leu  Asn  Leu  Thr
          165          170          175
Arg  Asn  Gly  Tyr  Gly  Ser  Thr  Gln  Tyr  Ile  Arg  Phe  Ser  Pro  Asp  Phe
          180          185          190
Thr  Phe  Gly  Phe  Glu  Glu  Ser  Leu  Glu  Val  Asp  Thr  Asn  Pro  Leu  Leu
          195          200          205
Gly  Ala  Gly  Lys  Phe  Ala  Thr  Asp  Pro  Ala  Val  Thr  Leu  Ala  His  Glu
          210          215          220
Leu  Ile  His  Ala  Gly  His  Arg  Leu  Tyr  Gly  Ile  Ala  Ile  Asn  Pro  Asn
          225          230          235          240
Arg  Val  Phe  Lys  Val  Asn  Thr  Asn  Ala  Tyr  Tyr  Glu  Met  Ser  Gly  Leu
          245          250          255
Glu  Val  Ser  Phe  Glu  Glu  Leu  Arg  Thr  Phe  Gly  Gly  His  Asp  Ala  Lys
          260          265          270
Phe  Ile  Asp  Ser  Leu  Gln  Glu  Asn  Glu  Phe  Arg  Leu  Tyr  Tyr  Tyr  Asn
          275          280          285
Lys  Phe  Lys  Asp  Ile  Ala  Ser  Thr  Leu  Asn  Lys  Ala  Lys  Ser  Ile  Val
          290          295          300
Gly  Thr  Thr  Ala  Ser  Leu  Gln  Tyr  Met  Lys  Asn  Val  Phe  Lys  Glu  Lys
          305          310          315          320
Tyr  Leu  Leu  Ser  Glu  Asp  Thr  Ser  Gly  Lys  Phe  Ser  Val  Asp  Lys  Leu
          325          330          335

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Lys	Phe	Asp	Lys 340	Leu	Tyr	Lys	Met	Leu 345	Thr	Glu	Ile	Tyr	Thr	Glu	Asp
Asn	Phe	Val 355	Lys	Phe	Phe	Lys	Val 360	Leu	Asn	Arg	Lys	Thr 365	Tyr	Leu	Asn
Phe	Asp 370	Lys	Ala	Val	Phe	Lys 375	Ile	Asn	Ile	Val	Pro 380	Lys	Val	Asn	Tyr
Thr 385	Ile	Tyr	Asp	Gly	Phe 390	Asn	Leu	Arg	Asn	Thr 395	Asn	Leu	Ala	Ala	Asn 400
Phe	Asn	Gly	Gln	Asn 405	Thr	Glu	Ile	Asn 410	Met	Asn	Phe	Thr	Lys 415	Leu	
Lys	Asn	Phe	Thr 420	Gly	Leu	Phe	Glu	Phe 425	Tyr	Lys	Leu	Leu	Cys 430	Val	Arg
Gly	Ile	Ile 435	Thr	Ser	Lys	Thr	Lys 440	Ser	Leu	Asp	Lys	Gly 445	Tyr	Asn	Lys
Ala	Leu 450	Asn	Asp	Leu	Cys	Ile 455	Lys	Val	Asn	Asn	Trp 460	Asp	Leu	Phe	Phe
Ser 465	Pro	Ser	Glu	Asp	Asn 470	Phe	Thr	Asn	Asp	Leu 475	Asn	Lys	Gly	Glu	Glu 480
Ile	Thr	Ser	Asp	Thr 485	Asn	Ile	Glu	Ala	Ala 490	Glu	Glu	Asn	Ile	Ser 495	Leu
Asp	Leu	Ile	Gln 500	Gln	Tyr	Tyr	Leu	Thr 505	Phe	Asn	Phe	Asp	Asn 510	Glu	Pro
Glu	Asn	Ile 515	Ser	Ile	Glu	Asn	Leu 520	Ser	Ser	Asp	Ile 525	Gly	Gln	Leu	
Glu	Leu 530	Met	Pro	Asn	Ile	Glu 535	Arg	Phe	Pro	Asn	Gly 540	Lys	Lys	Tyr	Glu
Leu 545	Asp	Lys	Tyr	Thr	Met 550	Phe	His	Tyr	Leu	Arg 555	Ala	Gln	Glu	Phe	Glu 560
His	Gly	Lys	Ser	Arg 565	Ile	Ala	Leu	Thr	Asn 570	Ser	Val	Asn	Glu	Ala 575	Leu
Leu	Asn	Pro	Ser 580	Arg	Val	Tyr	Thr	Phe 585	Phe	Ser	Ser	Asp	Tyr 590	Val	Lys
Lys	Val	Asn 595	Lys	Ala	Thr	Glu	Ala 600	Ala	Met	Phe	Leu	Gly 605	Trp	Val	Glu
Gln	Leu 610	Val	Tyr	Asp	Phe	Thr 615	Asp	Glu	Thr	Ser	Glu 620	Val	Ser	Thr	Thr
Asp 625	Lys	Ile	Ala	Asp	Ile 630	Thr	Ile	Ile	Ile	Pro 635	Tyr	Ile	Gly	Pro	Ala 640
Leu	Asn	Ile	Gly	Asn 645	Met	Leu	Tyr	Lys	Asp 650	Asp	Phe	Val	Gly	Ala 655	Leu
Ile	Phe	Ser	Gly 660	Ala	Val	Ile	Leu	Leu 665	Glu	Phe	Ile	Pro	Glu	Ile	Ala
Ile	Pro	Val 675	Leu	Gly	Thr	Phe	Ala 680	Leu	Val	Ser	Tyr	Ile 685	Ala	Asn	Lys

Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu  
690 695 700

Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys  
705 710 715 720

Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu  
725 730 735

Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn  
740 745 750

Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp  
755 760 765

Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile  
770 775 780

Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met  
785 790 795 800

Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys  
805 810 815

Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly  
820 825 830

Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp  
835 840 845

Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser  
850 855 860

Thr Phe Thr Glu Tyr Ile Lys  
865 870

## (2) INFORMATION FOR SEQ ID NO: 9:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2628 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..2628

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

ATG CAG TTC GTG AAC AAG CAG TTC AAC TAT AAG GAC CCT GTA AAC GGT	48
Met Gln Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly	
1 5 10 15	
GTT GAC ATT GCC TAC ATC AAA ATT CCA AAC GCC GGC CAG ATG CAG CCG	96
Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro	
20 25 30	
GTG AAG GCT TTC AAG ATT CAT AAC AAA ATC TGG GTT ATT CCG GAA CGC	144
Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg	
35 40 45	
GAT ACA TTT ACG AAC CCG GAA GAA GGA GAC TTG AAC CCG CCG CCG GAA	192
Asp Thr Phe Thr Asn Pro Glu Gly Asp Leu Asn Pro Pro Pro Glu	
50 55 60	



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GCA AAG CAG GTG CCA GTT TCA TAC TAC GAT TCA ACC TAT CTG AGC ACA Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr 65 70 75 80	240
GAC AAC GAG AAG GAT AAC TAC CTG AAG GGA GTG ACC AAA TTA TTC GAG Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu 85 90 95	288
CGT ATT TAT TCC ACT GAC CTG GGC CGT ATG CTG CTG ACC TCA ATC GTC Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val 100 105 110	336
CGC GGA ATC CCA TTT TGG GGT GGC AGT ACC ATT GAC ACG GAG TTG AAG Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys 115 120 125	384
GTT ATT GAC ACT AAC TGC ATT AAC GTG ATC CAA CCA GAC GGT AGC TAC Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr 130 135 140	432
AGA TCT GAA GAA CTT AAC CTC GTA ATC ATC GGG CCC TCC GCG GAC ATT Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile 145 150 155 160	480
ATC CAG TTT GAG TGC AAG AGC TTT GGC CAC GAA GTG TTG AAC CTG ACC Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr 165 170 175	528
CGT AAC GGT TAC GGC TCT ACT CAG TAC ATT CGT TTC AGC CCA GAC TTC Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe 180 185 190	576
ACG TTC GGT TTC GAG GAG AGC CTG GAG GTT GAT ACC AAC CCG CTG TTG Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu 195 200 205	624
GGT GCA GGC AAG TTC GCA ACT GAT CCA GCG GTG ACC CTG GCA CAC GAG Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu 210 215 220	672
CTG ATC CAC GCC GGT CAT CGT CTG TAT GGC ATT GCG ATT AAC CCG AAC Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn 225 230 235 240	720
CGC GTG TTC AAG GTT AAC ACC AAC GCC TAC TAC GAG ATG AGT GGT TTA Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu 245 250 255	768
GAA GTA AGC TTC GAG GAA CTG CGC ACG TTC GGT GGC CAT GAT GCG AAG Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys 260 265 270	816
TTT ATC GAC AGC TTG CAG GAG AAC GAG TTC CGT CTG TAC TAC TAC AAC Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn 275 280 285	864
AAG TTT AAA GAT ATT GCA AGT ACA CTG AAC AAG GCT AAG TCC ATT GTG Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser Ile Val 290 295 300	912
GGT ACC ACT GCT TCA TTA CAG TAT ATG AAA AAT GTT TTT AAA GAG AAA Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys Glu Lys 305 310 315 320	960
TAT CTC CTA TCT GAA GAT ACA TCT GGA AAA TTT TCG GTA GAT AAA TTA Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp Lys Leu 325 330 335	1008

AAA	TTT	GAT	AAG	TTA	TAC	AAA	ATG	TTA	ACA	GAG	ATT	TAC	ACA	GAG	GAT	1056
Lys	Phe	Asp	Lys	Leu	Tyr	Lys	Met	Leu	Thr	Glu	Ile	Tyr	Thr	Glu	Asp	
			340					345					350			
AAT	TTT	GTT	AAG	TTT	TTT	AAA	GTA	CTT	AAC	AGA	AAA	ACA	TAT	TTG	AAT	1104
Asn	Phe	Val	Lys	Phe	Phe	Lys	Val	Leu	Asn	Arg	Lys	Thr	Tyr	Leu	Asn	
		355					360					365				
TTT	GAT	AAA	GCC	GTA	TTT	AAG	ATA	AAT	ATA	GTA	CCT	AAG	GTA	AAT	TAC	1152
Phe	Asp	Lys	Ala	Val	Phe	Lys	Ile	Asn	Ile	Val	Pro	Lys	Val	Asn	Tyr	
	370					375					380					
ACA	ATA	TAT	GAT	GGA	TTT	AAT	TTA	AGA	AAT	ACA	AAT	TTA	GCA	GCA	AAC	1200
Thr	Ile	Tyr	Asp	Gly	Phe	Asn	Leu	Arg	Asn	Thr	Asn	Leu	Ala	Ala	Asn	
385					390					395					400	
TTT	AAT	GGT	CAA	AAT	ACA	GAA	ATT	AAT	AAT	ATG	AAT	TTT	ACT	AAA	CTA	1248
Phe	Asn	Gly	Gln	Asn	Thr	Glu	Ile	Asn	Asn	Met	Asn	Phe	Thr	Lys	Leu	
				405					410					415		
AAA	AAT	TTT	ACT	GGA	TTG	TTT	GAA	TTT	TAT	AAG	TTG	CTA	TGT	GTA	AGA	1296
Lys	Asn	Phe	Thr	Gly	Leu	Phe	Glu	Phe	Tyr	Lys	Leu	Leu	Cys	Val	Arg	
			420					425					430			
GGG	ATA	ATA	ACT	TCT	AAA	ACT	AAA	TCA	TTA	GAT	AAA	GGA	TAC	AAT	AAG	1344
Gly	Ile	Ile	Thr	Ser	Lys	Thr	Lys	Ser	Leu	Asp	Lys	Gly	Tyr	Asn	Lys	
		435					440					445				
AGC	GCT	GAT	GGG	GCA	TTA	AAT	GAT	TTA	TGT	ATC	AAA	GTT	AAT	AAT	TGG	1392
Ser	Ala	Asp	Gly	Ala	Leu	Asn	Asp	Leu	Cys	Ile	Lys	Val	Asn	Asn	Trp	
	450					455					460					
GAC	TTG	TTT	TTT	AGT	CCT	TCA	GAA	GAT	AAT	TTT	ACT	AAT	GAT	CTA	AAT	1440
Asp	Leu	Phe	Phe	Ser	Pro	Ser	Glu	Asp	Asn	Phe	Thr	Asn	Asp	Leu	Asn	
465					470					475					480	
AAA	GGA	GAA	GAA	ATT	ACA	TCT	GAT	ACT	AAT	ATA	GAA	GCA	GCA	GAA	GAA	1488
Lys	Gly	Glu	Glu	Ile	Thr	Ser	Asp	Thr	Asn	Ile	Glu	Ala	Ala	Glu	Glu	
				485					490					495		
AAT	ATT	AGT	TTA	GAT	TTA	ATA	CAA	CAA	TAT	TAT	TTA	ACC	TTT	AAT	TTT	1536
Asn	Ile	Ser	Leu	Asp	Leu	Ile	Gln	Gln	Tyr	Tyr	Leu	Thr	Phe	Asn	Phe	
			500					505					510			
GAT	AAT	GAA	CCT	GAA	AAT	ATT	TCA	ATA	GAA	AAT	CTT	TCA	AGT	GAC	ATT	1584
Asp	Asn	Glu	Pro	Glu	Asn	Ile	Ser	Ile	Glu	Asn	Leu	Ser	Ser	Asp	Ile	
		515				520						525				
ATA	GGC	CAA	TTA	GAA	CTT	ATG	CCT	AAT	ATA	GAA	AGA	TTT	CCT	AAT	GGA	1632
Ile	Gly	Gln	Leu	Glu	Leu	Met	Pro	Asn	Ile	Glu	Arg	Phe	Pro	Asn	Gly	
	530					535					540					
AAA	AAG	TAT	GAG	TTA	GAT	AAA	TAT	ACT	ATG	TTC	CAT	TAT	CTT	CGT	GCT	1680
Lys	Lys	Tyr	Glu	Leu	Asp	Lys	Tyr	Thr	Met	Phe	His	Tyr	Leu	Arg	Ala	
545					550					555					560	
CAA	GAA	TTT	GAA	CAT	GGT	AAA	TCT	AGG	ATT	GCT	TTA	ACA	AAT	TCT	GTT	1728
Gln	Glu	Phe	Glu	His	Gly	Lys	Ser	Arg	Ile	Ala	Leu	Thr	Asn	Ser	Val	
				565					570					575		
AAC	GAA	GCA	TTA	TTA	AAT	CCT	AGT	CGT	GTT	TAT	ACA	TTT	TTT	TCT	TCA	1776
Asn	Glu	Ala	Leu	Leu	Asn	Pro	Ser	Arg	Val	Tyr	Thr	Phe	Phe	Ser	Ser	
			580					585					590			
GAC	TAT	GTA	AAG	AAA	GTT	AAT	AAA	GCT	ACG	GAG	GCA	GCT	ATG	TTT	TTA	1824
Asp	Tyr	Val	Lys	Lys	Val	Asn	Lys	Ala	Thr	Glu	Ala	Ala	Met	Phe	Leu	
		595					600					605				

GGC Gly	TGG Trp	GTA Val	GAA Glu	CAA Gln	TTA Leu	GTA Val	TAT Tyr	GAT Asp	TTT Phe	ACC Thr	GAT Asp	GAA Glu	ACT Thr	AGC Ser	GAA Glu	1872
610						615					620					
GTA Val	AGT Ser	ACT Thr	ACG Thr	GAT Asp	AAA Lys	ATT Ile	GCG Ala	GAT Asp	ATA Ile	ACT Thr	ATA Ile	ATT Ile	ATT Ile	CCA Pro	TAT Tyr	1920
625					630					635					640	
ATA Ile	GGA Gly	CCT Pro	GCT Ala	TTA Leu	AAT Asn	ATA Ile	GGT Gly	AAT Asn	ATG Met	TTA Leu	TAT Tyr	AAA Lys	GAT Asp	GAT Asp	TTT Phe	1968
				645					650				655			
GTA Val	GGT Gly	GCT Ala	TTA Leu	ATA Ile	TTT Phe	TCA Ser	GGA Gly	GCT Ala	GTT Val	ATT Ile	CTG Leu	TTA Leu	GAA Glu	TTT Phe	ATA Ile	2016
			660					665					670			
CCA Pro	GAG Glu	ATT Ile	GCA Ala	ATA Ile	CCT Pro	GTA Val	TTA Leu	GGT Gly	ACT Thr	TTT Phe	GCA Ala	CTT Leu	GTA Val	TCA Ser	TAT Tyr	2064
		675					680					685				
ATT Ile	GCG Ala	AAT Asn	AAG Lys	GTT Val	CTA Leu	ACC Thr	GTT Val	CAA Gln	ACA Thr	ATA Ile	GAT Asp	AAT Asn	GCT Ala	TTA Leu	AGT Ser	2112
	690					695					700					
AAA Lys	AGA Arg	AAT Asn	GAA Glu	AAA Lys	TGG Trp	GAT Asp	GAG Glu	GTC Val	TAT Tyr	AAA Lys	TAT Tyr	ATA Ile	GTA Val	ACA Thr	AAT Asn	2160
705					710					715					720	
TGG Trp	TTA Leu	GCA Ala	AAG Lys	GTT Val	AAT Asn	ACA Thr	CAG Gln	ATT Ile	GAT Asp	CTA Leu	ATA Ile	AGA Arg	AAA Lys	AAA Lys	ATG Met	2208
				725					730					735		
AAA Lys	GAA Glu	GCT Ala	TTA Leu	GAA Glu	AAT Asn	CAA Gln	GCA Ala	GAA Glu	GCA Ala	ACA Thr	AAG Lys	GCT Ala	ATA Ile	ATA Ile	AAC Asn	2256
			740					745					750			
TAT Tyr	CAG Gln	TAT Tyr	AAT Asn	CAA Gln	TAT Tyr	ACT Thr	GAG Glu	GAA Glu	GAG Glu	AAA Lys	AAT Asn	AAT Asn	ATT Ile	AAT Asn	TTT Phe	2304
	755						760					765				
AAT Asn	ATT Ile	GAT Asp	GAT Asp	TTA Leu	AGT Ser	TCG Ser	AAA Lys	CTT Leu	AAT Asn	GAG Glu	TCT Ser	ATA Ile	AAT Asn	AAA Lys	GCT Ala	2352
	770					775					780					
ATG Met	ATT Ile	AAT Asn	ATA Ile	AAT Asn	AAA Lys	TTT Phe	TTG Leu	AAT Asn	CAA Gln	TGC Cys	TCT Ser	GTT Val	TCA Ser	TAT Tyr	TTA Leu	2400
	785				790					795					800	
ATG Met	AAT Asn	TCT Ser	ATG Met	ATC Ile	CCT Pro	TAT Tyr	GGT Gly	GTT Val	AAA Lys	CGG Arg	TTA Leu	GAA Glu	GAT Asp	TTT Phe	GAT Asp	2448
				805					810					815		
GCT Ala	AGT Ser	CTT Leu	AAA Lys	GAT Asp	GCA Ala	TTA Leu	TTA Leu	AAG Lys	TAT Tyr	ATA Ile	TAT Tyr	GAT Asp	AAT Asn	AGA Arg	GGA Gly	2496
			820					825					830			
ACT Thr	TTA Leu	ATT Ile	GGT Gly	CAA Gln	GTA Val	GAT Asp	AGA Arg	TTA Leu	AAA Lys	GAT Asp	AAA Lys	GTT Val	AAT Asn	AAT Asn	ACA Thr	2544
		835					840					845				
CTT Leu	AGT Ser	ACA Thr	GAT Asp	ATA Ile	CCT Pro	TTT Phe	CAG Gln	CTT Leu	TCC Ser	AAA Lys	TAC Val	GTA Val	GAT Asp	AAT Asn	CAA Gln	2592
	850					855					860					
AGA Arg	TTA Leu	TTA Leu	TCT Ser	ACA Thr	TTT Phe	ACT Thr	GAA Glu	TAT Tyr	ATT Ile	AAG Lys	TAA *					2628
865					870					875						

## (2) INFORMATION FOR SEQ ID NO: 10:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 876 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

```

Met Gln Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly
 1             5             10             15
Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro
      20             25             30
Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg
      35             40             45
Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro Pro Glu
      50             55             60
Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr
      65             70             75             80
Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu
      85             90
Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val
      100             105             110
Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys
      115             120             125
Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr
      130             135             140
Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile
      145             150             155             160
Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr
      165             170             175
Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe
      180             185             190
Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu
      195             200             205
Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu
      210             215             220
Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn
      225             230             235             240
Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu
      245             250             255
Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys
      260             265             270
Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn
      275             280             285
Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser Ile Val
      290             295             300

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Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys Glu Lys  
 305 310 315 320  
 Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp Lys Leu  
 325 330 335  
 Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr Glu Asp  
 340 345 350  
 Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr Leu Asn  
 355 360 365  
 Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val Asn Tyr  
 370 375 380  
 Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala Ala Asn  
 385 390 395 400  
 Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr Lys Leu  
 405 410 415  
 Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys Val Arg  
 420 425 430  
 Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Asp Lys Gly Tyr Asn Lys  
 435 440 445  
 Ser Ala Asp Gly Ala Leu Asn Asp Leu Cys Ile Lys Val Asn Asn Trp  
 450 455 460  
 Asp Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn  
 465 470 475 480  
 Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu  
 485 490 495  
 Asn Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe  
 500 505 510  
 Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile  
 515 520 525  
 Ile Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly  
 530 535 540  
 Lys Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala  
 545 550 555 560  
 Gln Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val  
 565 570 575  
 Asn Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe-Phe Ser Ser  
 580 585 590  
 Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu  
 595 600 605  
 Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu  
 610 615 620  
 Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr  
 625 630 635 640  
 Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe  
 645 650 655

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Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile  
660 665 670

Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr  
675 680 685

Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser  
690 695 700

Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn  
705 710 715 720

Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met  
725 730 735

Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn  
740 745 750

Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe  
755 760 765

Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala  
770 775 780

Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu  
785 790 795 800

Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp  
805 810 815

Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly  
820 825 830

Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr  
835 840 845

Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln  
850 855 860

Arg Leu Leu Ser Thr Phe Thr Glu Tyr Ile Lys \*  
865 870 875

## (2) INFORMATION FOR SEQ ID NO: 11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2637 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE\_TYPE: DNA (genomic)

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..2637

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

ATG CAG TTC GTG AAC AAG CAG TTC AAC TAT AAG GAC CCT GTA AAC GGT	48
Met Gln Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly	
1 5 10 15	
GTT GAC ATT GCC TAC ATC AAA ATT CCA AAC GCC GGC CAG ATG CAG CCG	96
Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro	
20 25 30	

GTG	AAG	GCT	TTC	AAG	ATT	CAT	AAC	AAA	ATC	TGG	GTT	ATT	CCG	GAA	CGC	144
Val	Lys	Ala	Phe	Lys	Ile	His	Asn	Lys	Ile	Trp	Val	Ile	Pro	Glu	Arg	
		35					40					45				
GAT	ACA	TTT	ACG	AAC	CCG	GAA	GAA	GGA	GAC	TTG	AAC	CCG	CCG	CCG	GAA	192
Asp	Thr	Phe	Thr	Asn	Pro	Glu	Glu	Gly	Asp	Leu	Asn	Pro	Pro	Pro	Glu	
		50				55					60					
GCA	AAG	CAG	GTG	CCA	GTT	TCA	TAC	TAC	GAT	TCA	ACC	TAT	CTG	AGC	ACA	240
Ala	Lys	Gln	Val	Pro	Val	Ser	Tyr	Tyr	Asp	Ser	Thr	Tyr	Leu	Ser	Thr	
		65			70					75					80	
GAC	AAC	GAG	AAG	GAT	AAC	TAC	CTG	AAG	GGA	GTG	ACC	AAA	TTA	TTC	GAG	288
Asp	Asn	Glu	Lys	Asp	Asn	Tyr	Leu	Lys	Gly	Val	Thr	Lys	Leu	Phe	Glu	
				85					90					95		
CGT	ATT	TAT	TCC	ACT	GAC	CTG	GGC	CGT	ATG	CTG	CTG	ACC	TCA	ATC	GTC	336
Arg	Ile	Tyr	Ser	Thr	Asp	Leu	Gly	Arg	Met	Leu	Leu	Thr	Ser	Ile	Val	
			100					105					110			
CGC	GGA	ATC	CCA	TTT	TGG	GGT	GGC	AGT	ACC	ATT	GAC	ACG	GAG	TTG	AAG	384
Arg	Gly	Ile	Pro	Phe	Trp	Gly	Gly	Ser	Thr	Ile	Asp	Thr	Glu	Leu	Lys	
		115					120					125				
GTT	ATT	GAC	ACT	AAC	TGC	ATT	AAC	GTG	ATC	CAA	CCA	GAC	GGT	AGC	TAC	432
Val	Ile	Asp	Thr	Asn	Cys	Ile	Asn	Val	Ile	Gln	Pro	Asp	Gly	Ser	Tyr	
		130				135					140					
AGA	TCT	GAA	GAA	CTT	AAC	CTC	GTA	ATC	ATC	GGG	CCC	TCC	GCG	GAC	ATT	480
Arg	Ser	Glu	Glu	Leu	Asn	Leu	Val	Ile	Ile	Gly	Pro	Ser	Ala	Asp	Ile	
		145			150					155					160	
ATC	CAG	TTT	GAG	TGC	AAG	AGC	TTT	GGC	CAC	GAA	GTG	TTG	AAC	CTG	ACG	528
Ile	Gln	Phe	Glu	Cys	Lys	Ser	Phe	Gly	His	Glu	Val	Leu	Asn	Leu	Thr	
				165				170						175		
CGT	AAC	GGT	TAC	GGC	TCT	ACT	CAG	TAC	ATT	CGT	TTC	AGC	CCA	GAC	TTC	576
Arg	Asn	Gly	Tyr	Gly	Ser	Thr	Gln	Tyr	Ile	Arg	Phe	Ser	Pro	Asp	Phe	
			180					185					190			
ACG	TTC	GGT	TTC	GAG	GAG	AGC	CTG	GAG	GTT	GAT	ACC	AAC	CCG	CTG	TTG	624
Thr	Phe	Gly	Phe	Glu	Glu	Ser	Leu	Glu	Val	Asp	Thr	Asn	Pro	Leu	Leu	
		195					200					205				
GGT	GCA	GGC	AAG	TTC	GCA	ACT	GAT	CCA	GCG	GTG	ACC	CTG	GCA	CAC	GAG	672
Gly	Ala	Gly	Lys	Phe	Ala	Thr	Asp	Pro	Ala	Val	Thr	Leu	Ala	His	Glu	
		210				215					220					
CTG	ATC	CAC	GCC	GGT	CAT	CGT	CTG	TAT	GGC	ATT	GCG	ATT	AAC	CCG	AAC	720
Leu	Ile	His	Ala	Gly	His	Arg	Leu	Tyr	Gly	Ile	Ala	Ile	Asn	Pro	Asn	
				225		230			235						240	
CGC	GTG	TTC	AAG	GTT	AAC	ACC	AAC	GCC	TAC	TAC	GAG	ATG	AGT	GGT	TTA	768
Arg	Val	Phe	Lys	Val	Asn	Thr	Asn	Ala	Tyr	Tyr	Glu	Met	Ser	Gly	Leu	
				245				250						255		
GAA	GTA	AGC	TTC	GAG	GAA	CTG	CGC	ACG	TTC	GGT	GGC	CAT	GAT	GCG	AAG	816
Glu	Val	Ser	Phe	Glu	Glu	Leu	Arg	Thr	Phe	Gly	Gly	His	Asp	Ala	Lys	
			260					265					270			
TTT	ATC	GAC	AGC	TTG	CAG	GAG	AAC	GAG	TTC	CGT	CTG	TAC	TAC	TAC	AAC	864
Phe	Ile	Asp	Ser	Leu	Gln	Glu	Asn	Glu	Phe	Arg	Leu	Tyr	Tyr	Tyr	Asn	
		275					280					285				
AAG	TTT	AAA	GAT	ATT	GCA	AGT	ACA	CTG	AAC	AAG	GCT	AAG	TCC	ATT	GTG	912
Lys	Phe	Lys	Asp	Ile	Ala	Ser	Thr	Leu	Asn	Lys	Ala	Lys	Ser	Ile	Val	
		290				295					300					

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GGT Gly 305	ACC Thr	ACT Thr	GCT Ala	TCA Ser	TTA Leu 310	CAG Gln	TAT Tyr	ATG Met	AAA Lys	AAT Asn 315	GTT Val	TTT Phe	AAA Lys	GAG Glu	AAA Lys 320	960
TAT Tyr	CTC Leu	CTA Leu	TCT Ser	GAA Glu 325	GAT Asp	ACA Thr	TCT Ser	GGA Gly	AAA Lys 330	TTT Phe	TCG Ser	GTA Val	GAT Asp	AAA Lys 335	TTA Leu	1008
AAA Lys	TTT Phe	GAT Asp	AAG Lys 340	TTA Leu	TAC Tyr	AAA Lys	ATG Met	TTA Leu 345	ACA Thr	GAG Glu	ATT Ile	TAC Tyr	ACA Thr	GAG Glu 350	GAT Asp	1056
AAT Asn	TTT Phe	GTT Val 355	AAG Lys	TTT Phe	TTT Phe	AAA Lys	GTA Val 360	CTT Leu	AAC Asn	AGA Arg	AAA Lys	ACA Thr	TAT Tyr	TTG Leu 365	AAT Asn	1104
TTT Phe 370	GAT Asp	AAA Lys	GCC Ala	GTA Val	TTT Phe	AAG Lys 375	ATA Ile	AAT Asn	ATA Ile	GTA Val	CCT Pro 380	AAG Lys	GTA Val	AAT Asn	TAC Tyr	1152
ACA Thr 385	ATA Ile	TAT Tyr	GAT Asp	GGA Gly	TTT Phe 390	AAT Asn	TTA Leu	AGA Arg	AAT Asn	ACA Thr 395	AAT Asn	TTA Leu	GCA Ala	GCA Ala	AAC Asn 400	1200
TTT Phe	AAT Asn	GGT Gly	CAA Gln 405	AAT Asn	ACA Thr	GAA Glu	ATT Ile	AAT Asn	AAT Asn 410	ATG Met	AAT Asn	TTT Phe	ACT Thr	AAA Lys 415	CTA Leu	1248
AAA Lys	AAT Asn	TTT Phe	ACT Thr 420	GGA Gly	TTG Leu	TTT Phe	GAA Glu 425	TTT Phe	TAT Tyr	AAG Lys	TTG Leu	CTA Leu	TGT Cys 430	GTA Val	AGA Arg	1296
GGG Gly	ATA Ile 435	ATA Ile	ACT Thr	TCT Ser	AAA Lys	ACT Thr 440	AAA Lys	TCA Ser	TTA Leu	GAT Asp	AAA Lys	GGA Gly 445	TAC Tyr	AAT Asn	AAG Lys	1344
ATC Ile 450	GAA Glu	GGT Gly	CGT Arg	TGC Cys	GAT Asp	GGG Gly 455	GCA Ala	TTA Leu	AAT Asn	GAT Asp	TTA Leu	TGT Cys	ATC Ile	AAA Lys	GTT Val	1392
AAT Asn 465	AAT Asn	TGG Trp	GAC Asp	TTG Leu	TTT Phe	TTT Phe	AGT Ser	CCT Pro	TCA Ser	GAA Glu 475	GAT Asp	AAT Asn	TTT Phe	ACT Thr	AAT Asn 480	1440
GAT Asp	CTA Leu	AAT Asn	AAA Lys	GGA Gly 485	GAA Glu	GAA Glu	ATT Ile	ACA Thr	TCT Ser	GAT Asp	ACT Thr	AAT Asn	ATA Ile	GAA Glu 495	GCA Ala	1488
GCA Ala	GAA Glu	GAA Glu	AAT Asn 500	ATT Ile	AGT Ser	TTA Leu	GAT Asp	TTA Leu 505	ATA Ile	CAA Gln	CAA Gln	TAT Tyr	TAT Tyr	TTA Leu 510	ACC Thr	1536
TTT Phe	AAT Asn	TTT Phe 515	GAT Asp	AAT Asn	GAA Glu	CCT Pro	GAA Glu 520	AAT Asn	ATT Ile	TCA Ser	ATA Ile	GAA Glu 525	AAT Asn	CTT Leu	TCA Ser	1584
AGT Ser 530	GAC Asp	ATT Ile	ATA Ile	GGC Gly	CAA Gln	TTA Leu 535	GAA Glu	CTT Leu	ATG Met	CCT Pro	AAT Asn 540	ATA Ile	GAA Glu	AGA Arg	TTT Phe	1632
CCT Pro 545	AAT Asn	GGA Gly	AAA Lys	AAG Lys	TAT Tyr 550	GAG Glu	TTA Leu	GAT Asp	AAA Lys	TAT Tyr 555	ACT Thr	ATG Met	TTC Phe	CAT His	TAT Tyr 560	1680
CTT Leu	CGT Arg	GCT Ala	CAA Gln	GAA Glu 565	TTT Phe	GAA Glu	CAT His	GGT Gly	AAA Lys 570	TCT Ser	AGG Arg	ATT Ile	GCT Ala	TTA Leu 575	ACA Thr	1728



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AAT TCT GTT AAC GAA GCA TTA TTA AAT CCT AGT CGT GTT TAT ACA TTT Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe 580 585 590	1776
TTT TCT TCA GAC TAT GTA AAG AAA GTT AAT AAA GCT ACG GAG GCA GCT Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala 595 600 605	1824
ATG TTT TTA GGC TGG GTA GAA CAA TTA GTA TAT GAT TTT ACC GAT GAA Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu 610 615 620	1872
ACT AGC GAA GTA AGT ACT ACG GAT AAA ATT GCG GAT ATA ACT ATA ATT Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile 625 630 635 640	1920
ATT CCA TAT ATA GGA CCT GCT TTA AAT ATA GGT AAT ATG TTA TAT AAA Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys 645 650 655	1968
GAT GAT TTT GTA GGT GCT TTA ATA TTT TCA GGA GCT GTT ATT CTG TTA Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu 660 665 670	2016
GAA TTT ATA CCA GAG ATT GCA ATA CCT GTA TTA GGT ACT TTT GCA CTT Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu 675 680 685	2064
GTA TCA TAT ATT GCG AAT AAG GTT CTA ACC GTT CAA ACA ATA GAT AAT Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn 690 695 700	2112
GCT TTA AGT AAA AGA AAT GAA AAA TGG GAT GAG GTC TAT AAA TAT ATA Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile 705 710 715 720	2160
GTA ACA AAT TGG TTA GCA AAG GTT AAT ACA CAG ATT GAT CTA ATA AGA Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg 725 730 735	2208
AAA AAA ATG AAA GAA GCT TTA GAA AAT CAA GCA GAA GCA ACA AAG GCT Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala 740 745 750	2256
ATA ATA AAC TAT CAG TAT AAT CAA TAT ACT GAG GAA GAG AAA AAT AAT Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Lys Lys Asn Asn 755 760 765	2304
ATT AAT TTT AAT ATT GAT GAT TTA AGT TCG AAA CTT AAT GAG TCT ATA Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile 770 775 780	2352
AAT AAA GCT ATG ATT AAT ATA AAT AAA TTT TTG AAT CAA TGC TCT GTT Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val 785 790 795 800	2400
TCA TAT TTA ATG AAT TCT ATG ATC CCT TAT GGT GTT AAA CGG TTA GAA Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu 805 810 815	2448
GAT TTT GAT GCT AGT CTT AAA GAT GCA TTA TTA AAG TAT ATA TAT GAT Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp 820 825 830	2496
AAT AGA GGA ACT TTA ATT GGT CAA GTA GAT AGA TTA AAA GAT AAA GTT Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val 835 840 845	2544

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AAT AAT ACA CTT AGT ACA GAT ATA CCT TTT CAG CTT TCC AAA TAC GTA 2592  
 Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val  
 850 855 860

GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TAA 2637  
 Asp Asn Gln Arg Leu Leu Ser Thr Phe Thr Glu Tyr Ile Lys \*  
 865 870 875

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 879 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Met Gln Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly  
 1 5 10 15  
 Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro  
 20 25 30  
 Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg  
 35 40 45  
 Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro Pro Glu  
 50 55 60  
 Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr  
 65 70 75 80  
 Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu  
 85 90 95  
 Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val  
 100 105 110  
 Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys  
 115 120 125  
 Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr  
 130 135 140  
 Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile  
 145 150 155 160  
 Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr  
 165 170 175  
 Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe  
 180 185 190  
 Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu  
 195 200 205  
 Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu  
 210 215 220  
 Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn  
 225 230 235 240  
 Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu  
 245 250 255

Glu	Val	Ser	Phe	Glu	Glu	Leu	Arg	Thr	Phe	Gly	Gly	His	Ala	Lys
			260					265					270	
Phe	Ile	Asp	Ser	Leu	Gln	Glu	Asn	Glu	Phe	Arg	Leu	Tyr	Tyr	Asn
		275					280					285		
Lys	Phe	Lys	Asp	Ile	Ala	Ser	Thr	Leu	Asn	Lys	Ala	Lys	Ser	Val
	290					295					300			
Gly	Thr	Thr	Ala	Ser	Leu	Gln	Tyr	Met	Lys	Asn	Val	Phe	Lys	Glu
305					310					315				320
Tyr	Leu	Leu	Ser	Glu	Asp	Thr	Ser	Gly	Lys	Phe	Ser	Val	Asp	Lys
				325					330					335
Lys	Phe	Asp	Lys	Leu	Tyr	Lys	Met	Leu	Thr	Glu	Ile	Tyr	Thr	Glu
			340					345					350	Asp
Asn	Phe	Val	Lys	Phe	Phe	Lys	Val	Leu	Asn	Arg	Lys	Thr	Tyr	Leu
		355					360					365		Asn
Phe	Asp	Lys	Ala	Val	Phe	Lys	Ile	Asn	Ile	Val	Pro	Lys	Val	Tyr
	370					375					380			
Thr	Ile	Tyr	Asp	Gly	Phe	Asn	Leu	Arg	Asn	Thr	Asn	Leu	Ala	Ala
385					390					395				Asn
Phe	Asn	Gly	Gln	Asn	Thr	Glu	Ile	Asn	Asn	Met	Asn	Phe	Thr	Lys
				405					410					415
Lys	Asn	Phe	Thr	Gly	Leu	Phe	Glu	Phe	Tyr	Lys	Leu	Leu	Cys	Val
			420					425					430	Arg
Gly	Ile	Ile	Thr	Ser	Lys	Thr	Lys	Ser	Leu	Asp	Lys	Gly	Tyr	Asn
		435					440					445		Lys
Ile	Glu	Gly	Arg	Cys	Asp	Gly	Ala	Leu	Asn	Asp	Leu	Cys	Ile	Lys
	450					455					460			Val
Asn	Asn	Trp	Asp	Leu	Phe	Phe	Ser	Pro	Ser	Glu	Asp	Asn	Phe	Thr
465					470					475				Asn
Asp	Leu	Asn	Lys	Gly	Glu	Glu	Ile	Thr	Ser	Asp	Thr	Asn	Ile	Glu
				485					490					495
Ala	Glu	Glu	Asn	Ile	Ser	Leu	Asp	Leu	Ile	Gln	Gln	Tyr	Tyr	Leu
			500					505					510	Thr
Phe	Asn	Phe	Asp	Asn	Glu	Pro	Glu	Asn	Ile	Ser	Ile	Glu	Asn	Leu
		515					520					525		Ser
Ser	Asp	Ile	Ile	Gly	Gln	Leu	Glu	Leu	Met	Pro	Asn	Ile	Glu	Arg
	530					535					540			Phe
Pro	Asn	Gly	Lys	Lys	Tyr	Glu	Leu	Asp	Lys	Tyr	Thr	Met	Phe	His
545					550					555				Tyr
Leu	Arg	Ala	Gln	Glu	Phe	Glu	His	Gly	Lys	Ser	Arg	Ile	Ala	Leu
				565					570					575
Asn	Ser	Val	Asn	Glu	Ala	Leu	Leu	Asn	Pro	Ser	Arg	Val	Tyr	Thr
			580					585					590	Phe
Phe	Ser	Ser	Asp	Tyr	Val	Lys	Lys	Val	Asn	Lys	Ala	Thr	Glu	Ala
		595					600					605		Ala

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Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu
 610                      615                      620

Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile
625                      630                      635                      640

Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys
                      645                      650                      655

Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu
                      660                      665                      670

Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu
                      675                      680                      685

Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn
690                      695                      700

Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile
705                      710                      715                      720

Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg
725                      730                      735

Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala
740                      745                      750

Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn
755                      760                      765

Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile
770                      775                      780

Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val
785                      790                      795                      800

Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu
805                      810                      815

Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp
820                      825                      830

Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val
835                      840                      845

Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val
850                      855                      860

Asp Asn Gln Arg Leu Leu Ser Thr Phe Thr Glu Tyr Ile Lys *
865                      870                      875

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## (2) INFORMATION FOR SEQ ID NO: 13:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2862 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..2862

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

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ATG CAG TTC GTG AAC AAG CAG TTC AAC TAT AAG GAC CCT GTA AAC GGT Met Gln Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly 1 5 10 15	48
GTT GAC ATT GCC TAC ATC AAA ATT CCA AAC GCC GGC CAG ATG CAG CCG Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro 20 25 30	96
GTG AAG GCT TTC AAG ATT CAT AAC AAA ATC TGG GTT ATT CCG GAA CGC Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg 35 40 45	144
GAT ACA TTT ACG AAC CCG GAA GAA GGA GAC TTG AAC CCG CCG CCG GAA Asp Thr Phe Thr Asn Pro Glu Gly Asp Leu Asn Pro Pro Pro Glu 50 55 60	192
GCA AAG CAG GTG CCA GTT TCA TAC TAC GAT TCA ACC TAT CTG AGC ACA Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr 65 70 75 80	240
GAC AAC GAG AAG GAT AAC TAC CTG AAG GGA GTG ACC AAA TTA TTC GAG Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu 85 90 95	288
CGT ATT TAT TCC ACT GAC CTG GGC CGT ATG CTG CTG ACC TCA ATC GTC Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val 100 105 110	336
CGC GGA ATC CCA TTT TGG GGT GGC AGT ACC ATT GAC ACG GAG TTG AAG Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys 115 120 125	384
GTT ATT GAC ACT AAC TGC ATT AAC GTG ATC CAA CCA GAC GGT AGC TAC Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr 130 135 140	432
AGA TCT GAA GAA CTT AAC CTC GTA ATC ATC GGG CCC TCC GCG GAC ATT Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile 145 150 155 160	480
ATC CAG TTT GAG TGC AAG AGC TTT GGC CAC GAA GTG TTG AAC CTG ACG Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr 165 170 175	528
CGT AAC GGT TAC GGC TCT ACT CAG TAC ATT CGT TTC AGC CCA GAC TTC Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe 180 185 190	576
ACG TTC GGT TTC GAG GAG AGC CTG GAG GTT GAT ACC AAC CCG CTG TTG Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu 195 200 205	624
GGT GCA GGC AAG TTC GCA ACT GAT CCA GCG GTG ACC CTG GCA CAC GAG Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu 210 215 220	672
CTG ATC CAC GCC GGT CAT CGT CTG TAT GGC ATT GCG ATT AAC CCG AAC Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn 225 230 235 240	720
CGC GTG TTC AAG GTT AAC ACC AAC GCC TAC TAC GAG ATG AGT GGT TTA Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu 245 250 255	768
GAA GTA AGC TTC GAG GAA CTG CGC ACG TTC GGT GGC CAT GAT GCG AAG Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys 260 265 270	816

TTT Phe	ATC Ile	GAC Asp 275	AGC Ser	TTG Leu	CAG Gln	GAG Glu	AAC Asn 280	GAG Glu	TTC Phe	CGT Arg	CTG Leu	TAC Tyr 285	TAC Tyr	TAC Tyr	AAC Asn	864
AAG Lys	TTT Phe 290	AAA Lys	GAT Asp	ATT Ile	GCA Ala	AGT Ser 295	ACA Thr	CTG Leu	AAC Asn	AAG Lys	GCT Ala 300	AAG Lys	TCC Ser	ATT Ile	GTG Val	912
GGT Gly 305	ACC Thr	ACT Thr	GCT Ala	TCA Ser	TTA Leu 310	CAG Gln	TAT Tyr	ATG Met	AAA Lys	AAT Asn 315	GTT Val	TTT Phe	AAA Lys	GAG Glu	AAA Lys 320	960
TAT Tyr	CTC Leu	CTA Leu	TCT Ser	GAA Glu 325	GAT Asp	ACA Thr	TCT Ser	GGA Gly	AAA Lys 330	TTT Phe	TCG Ser	GTA Val	GAT Asp	AAA Lys 335	TTA Leu	1008
AAA Lys	TTT Phe	GAT Asp	AAG Lys 340	TTA Leu	TAC Tyr	AAA Lys	ATG Met	TTA Leu 345	ACA Thr	GAG Glu	ATT Ile	TAC Tyr	ACA Thr 350	GAG Glu	GAT Asp	1056
AAT Asn	TTT Phe	GTT Val 355	AAG Lys	TTT Phe	TTT Phe	AAA Lys	GTA Val 360	CTT Leu	AAC Asn	AGA Arg	AAA Lys	ACA Thr 365	TAT Tyr	TTG Leu	AAT Asn	1104
TTT Phe	GAT Asp 370	AAA Lys	GCC Ala	GTA Val	TTT Phe	AAG Lys 375	ATA Ile	AAT Asn	ATA Ile	GTA Val	CCT Pro 380	AAG Lys	GTA Val	AAT Asn	TAC Tyr	1152
ACA Thr 385	ATA Ile	TAT Tyr	GAT Asp	GGA Gly	TTT Phe 390	AAT Asn	TTA Leu	AGA Arg	AAT Asn	ACA Thr 395	AAT Asn	TTA Leu	GCA Ala	GCA Ala	AAC Asn 400	1200
TTT Phe	AAT Asn	GGT Gly	CAA Gln	AAT Asn 405	ACA Thr	GAA Glu	ATT Ile	AAT Asn	AAT Asn 410	ATG Met	AAT Asn	TTT Phe	ACT Thr	AAA Lys 415	CTA Leu	1248
AAA Lys	AAT Asn	TTT Phe	ACT Thr 420	GGA Gly	TTG Leu	TTT Phe	GAA Glu	TTT Phe 425	TAT Tyr	AAG Lys	TTG Leu	CTA Leu	TGT Cys 430	GTA Val	AGA Arg	1296
GGG Gly	ATA Ile	ATA Ile 435	ACT Thr	TCT Ser	AAA Lys	ACT Thr	AAA Lys 440	TCA Ser	TTA Leu	GAT Asp	AAA Lys	GGA Gly 445	TAC Tyr	AAT Asn	AAG Lys	1344
ATC Ile	GAA Glu 450	GGT Gly	CGT Arg	TGC Cys	GAT Asp	GGG Gly 455	GCA Ala	TTA Leu	AAT Asn	GAT Asp	TTA Leu 460	TGT Cys	ATC Ile	AAA Lys	GTT Val	1392
AAT Asn 465	AAT Asn	TGG Trp	GAC Asp	TTG Leu	TTT Phe 470	TTT Phe	AGT Ser	CCT Pro	TCA Ser	GAA Glu 475	GAT Asp	AAT Asn	TTT Phe	ACT Thr	AAT Asn 480	1440
GAT Asp	CTA Leu	AAT Asn	AAA Lys	GGA Gly 485	GAA Glu	GAA Glu	ATT Ile	ACA Thr	TCT Ser 490	GAT Asp	ACT Thr	AAT Asn	ATA Ile	GAA Glu 495	GCA Ala	1488
GCA Ala	GAA Glu	GAA Glu	AAT Asn 500	ATT Ile	AGT Ser	TTA Leu	GAT Asp	TTA Leu 505	ATA Ile	CAA Gln	CAA Gln	TAT Tyr	TAT Tyr 510	TTA Leu	ACC Thr	1536
TTT Phe	AAT Asn	TTT Phe 515	GAT Asp	AAT Asn	GAA Glu	CCT Pro	GAA Glu 520	AAT Asn	ATT Ile	TCA Ser	ATA Ile	GAA Glu 525	AAT Asn	CTT Leu	TCA Ser	1584
AGT Ser	GAC Asp 530	ATT Ile	ATA Ile	GGC Gly	CAA Gln	TTA Leu 535	GAA Glu	CTT Leu	ATG Met	CCT Pro	AAT Asn 540	ATA Ile	GAA Glu	AGA Arg	TTT Phe	1632

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CCT Pro 545	AAT Asn 545	GGA Gly 545	AAA Lys 545	AAG Lys 545	TAT Tyr 550	GAG Glu 550	TTA Leu 550	GAT Asp 550	AAA Lys 555	TAT Tyr 555	ACT Thr 555	ATG Met 555	TTC Phe 555	CAT His 555	TAT Tyr 560	1680
CTT Leu 565	CGT Arg 565	GCT Ala 565	CAA Gln 565	GAA Glu 565	TTT Phe 565	GAA Glu 565	CAT His 565	GGT Gly 570	AAA Lys 570	TCT Ser 570	AGG Arg 570	ATT Ile 570	GCT Ala 575	TTA Leu 575	ACA Thr 575	1728
AAT Asn 580	TCT Ser 580	GTT Val 580	AAC Asn 580	GAA Glu 580	GCA Ala 580	TTA Leu 580	TTA Leu 580	AAT Asn 585	CCT Pro 585	AGT Ser 585	CGT Arg 585	GTT Val 585	TAT Tyr 590	ACA Thr 590	TTT Phe 590	1776
TTT Phe 595	TCT Ser 595	TCA Ser 595	GAC Asp 595	TAT Tyr 595	GTA Val 595	AAG Lys 595	AAA Lys 600	GTT Val 600	AAT Asn 600	AAA Lys 600	GCT Ala 605	ACG Thr 605	GAG Glu 605	GCA Ala 605	GCT Ala 605	1824
ATG Met 610	TTT Phe 610	TTA Leu 610	GGC Gly 610	TGG Trp 610	GTA Val 615	GAA Glu 615	CAA Gln 615	TTA Leu 615	GTA Val 615	TAT Tyr 615	GAT Asp 620	TTT Phe 620	ACC Thr 620	GAT Asp 620	GAA Glu 620	1872
ACT Thr 625	AGC Ser 625	GAA Glu 625	GTA Val 625	AGT Ser 625	ACT Thr 630	ACG Thr 630	GAT Asp 630	AAA Lys 630	ATT Ile 630	GCG Ala 635	GAT Asp 635	ATA Ile 635	ACT Thr 635	ATA Ile 635	ATT Ile 640	1920
ATT Ile 645	CCA Pro 645	TAT Tyr 645	ATA Ile 645	GGA Gly 645	CCT Pro 645	GCT Ala 645	TTA Leu 645	AAT Asn 650	ATA Ile 650	GGT Gly 650	AAT Asn 650	ATG Met 650	TTA Leu 655	TAT Tyr 655	AAA Lys 655	1968
GAT Asp 660	GAT Asp 660	TTT Phe 660	GTA Val 660	GGT Gly 660	GCT Ala 660	TTA Leu 660	ATA Ile 660	TTT Phe 665	TCA Ser 665	GGA Gly 665	GCT Ala 665	GTT Val 665	ATT Ile 670	CTG Leu 670	TTA Leu 670	2016
GAA Glu 675	TTT Phe 675	ATA Ile 675	CCA Pro 675	GAG Glu 675	ATT Ile 675	GCA Ala 675	ATA Ile 675	CCT Pro 680	GTA Val 680	TTA Leu 680	GGT Gly 685	ACT Thr 685	TTT Phe 685	GCA Ala 685	CTT Leu 685	2064
GTA Val 690	TCA Ser 690	TAT Tyr 690	ATT Ile 690	GCG Ala 690	AAT Asn 695	AAG Lys 695	GTT Val 695	CTA Leu 695	ACC Thr 695	GTT Val 695	CAA Gln 700	ACA Thr 700	ATA Ile 700	GAT Asp 700	AAT Asn 700	2112
GCT Ala 705	TTA Leu 705	AGT Ser 705	AAA Lys 705	AGA Arg 710	AAT Asn 710	GAA Glu 710	AAA Lys 710	TGG Trp 715	GAT Asp 715	GAG Glu 715	GTC Val 715	TAT Tyr 715	AAA Lys 715	TAT Tyr 720	ATA Ile 720	2160
GTA Val 725	ACA Thr 725	AAT Asn 725	TGG Trp 725	TTA Leu 725	GCA Ala 725	AAG Lys 725	GTT Val 725	AAT Asn 730	ACA Thr 730	CAG Gln 730	ATT Ile 730	GAT Asp 730	CTA Leu 735	ATA Ile 735	AGA Arg 735	2208
AAA Lys 740	AAA Lys 740	ATG Met 740	AAA Lys 740	GAA Glu 740	GCT Ala 740	TTA Leu 740	GAA Glu 745	AAT Asn 745	CAA Gln 745	GCA Ala 745	GAA Glu 745	GCA Ala 745	ACA Thr 750	AAG Lys 750	GCT Ala 750	2256
ATA Ile 755	ATA Ile 755	AAC Asn 755	TAT Tyr 755	CAG Gln 755	TAT Tyr 755	AAT Asn 755	CAA Gln 760	TAT Tyr 760	ACT Thr 760	GAG Glu 765	GAA Glu 765	GAG Glu 765	AAA Lys 765	AAT Asn 765	AAT Asn 765	2304
ATT Ile 770	AAT Asn 770	TTT Phe 770	AAT Asn 770	ATT Ile 770	GAT Asp 775	GAT Asp 775	TTA Leu 775	AGT Ser 775	TCG Ser 775	AAA Lys 780	CTT Leu 780	AAT Asn 780	GAG Glu 780	TCT Ser 780	ATA Ile 780	2352
AAT Asn 785	AAA Lys 785	GCT Ala 785	ATG Met 785	ATT Ile 785	AAT Asn 790	ATA Ile 790	AAT Asn 790	AAA Lys 795	TTT Phe 795	TTG Leu 795	AAT Asn 795	CAA Gln 795	TGC Cys 795	TCT Ser 800	GTT Val 800	2400
TCA Ser 805	TAT Tyr 805	TTA Leu 805	ATG Met 805	AAT Asn 805	TCT Ser 805	ATG Met 805	ATC Ile 805	CCT Pro 810	TAT Tyr 810	GGT Gly 810	GTT Val 810	AAA Lys 810	CGG Arg 810	TTA Leu 815	GAA Glu 815	2448

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GAT TTT GAT GCT AGT CTT AAA GAT GCA TTA TTA AAG TAT ATA TAT GAT Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp	2496
820 825 830	
AAT AGA GGA ACT TTA ATT GGT CAA GTA GAT AGA TTA AAA GAT AAA GTT Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val	2544
835 840 845	
AAT AAT ACA CTT AGT ACA GAT ATA CCT TTT CAG CTT TCC AAA TAC GTA Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val	2592
850 855 860	
GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TCT AGG Asp Asn Gln Arg Leu Leu Ser Thr Phe Thr Glu Tyr Ile Lys Ser Arg	2640
865 870 875 880	
CCT GGA CCG GAG ACG CTC TGC GGG GCT GAG CTG GTG GAT GCT CTT CAG Pro Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln	2688
885 890 895	
TTC GTG TGT GGA GAC AGG GGC TTT TAT TTC AAC AAG CCC ACA GGG TAT Phe Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr	2736
900 905 910	
GGC TCC AGC AGT CGG AGG GCG CCT CAG ACA GGT ATC GTG GAT GAG TGC Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys	2784
915 920 925	
TGC TTC CGG AGC TGT GAT CTA AGG AGG CTG GAG ATG TAT TGC GCA CCC Cys Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro	2832
930 935 940	
CTC AAG CCT GCC AAG TCA GCT GAA GCT TAG Leu Lys Pro Ala Lys Ser Ala Glu Ala *	2862
945 950	

## (2) INFORMATION FOR SEQ ID NO: 14:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 954 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Met Gln Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly 1 5 10 15	
Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro 20 25 30	
Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg 35 40 45	
Asp Thr Phe Thr Asn Pro Glu Gly Asp Leu Asn Pro Pro Pro Glu 50 55 60	
Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr 65 70 75 80	
Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu 85 90 95	
Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val 100 105 110	



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Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys  
 115 120 125  
 Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr  
 130 135 140  
 Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile  
 145 150 155 160  
 Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr  
 165 170 175  
 Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe  
 180 185 190  
 Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu  
 195 200 205  
 Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu  
 210 215 220  
 Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn  
 225 230 235 240  
 Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu  
 245 250 255  
 Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys  
 260 265 270  
 Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn  
 275 280 285  
 Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser Ile Val  
 290 295 300  
 Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys Glu Lys  
 305 310 315 320  
 Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp Lys Leu  
 325 330 335  
 Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr Glu Asp  
 340 345 350  
 Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr Leu Asn  
 355 360 365  
 Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val Asn Tyr  
 370 375 380  
 Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala Ala Asn  
 385 390 395 400  
 Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr Lys Leu  
 405 410 415  
 Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys Val Arg  
 420 425 430  
 Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Asp Lys Gly Tyr Asn Lys  
 435 440 445  
 Ile Glu Gly Arg Cys Asp Gly Ala Leu Asn Asp Leu Cys Ile Lys Val  
 450 455 460

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Asn 465	Asn	Trp	Asp	Leu	Phe 470	Phe	Ser	Pro	Ser	Glu 475	Asp	Asn	Phe	Thr	Asn 480
Asp	Leu	Asn	Lys	Gly 485	Glu	Glu	Ile	Thr	Ser 490	Asp	Thr	Asn	Ile	Glu	Ala 495
Ala	Glu	Glu	Asn 500	Ile	Ser	Leu	Asp	Leu 505	Ile	Gln	Gln	Tyr	Tyr 510	Leu	Thr
Phe	Asn	Phe 515	Asp	Asn	Glu	Pro	Glu 520	Asn	Ile	Ser	Ile	Glu 525	Asn	Leu	Ser
Ser	Asp 530	Ile	Ile	Gly	Gln	Leu 535	Glu	Leu	Met	Pro	Asn 540	Ile	Glu	Arg	Phe
Pro 545	Asn	Gly	Lys	Lys	Tyr 550	Glu	Leu	Asp	Lys	Tyr 555	Thr	Met	Phe	His	Tyr 560
Leu	Arg	Ala	Gln	Glu 565	Phe	Glu	His	Gly	Lys 570	Ser	Arg	Ile	Ala	Leu	Thr 575
Asn	Ser	Val	Asn 580	Glu	Ala	Leu	Leu	Asn 585	Pro	Ser	Arg	Val	Tyr 590	Thr	Phe
Phe	Ser	Ser 595	Asp	Tyr	Val	Lys	Lys 600	Val	Asn	Lys	Ala	Thr 605	Glu	Ala	Ala
Met	Phe 610	Leu	Gly	Trp	Val	Glu 615	Gln	Leu	Val	Tyr	Asp 620	Phe	Thr	Asp	Glu
Thr 625	Ser	Glu	Val	Ser	Thr 630	Thr	Asp	Lys	Ile	Ala 635	Asp	Ile	Thr	Ile	Ile 640
Ile	Pro	Tyr	Ile	Gly 645	Pro	Ala	Leu	Asn 650	Ile	Gly	Asn	Met	Leu	Tyr	Lys 655
Asp	Asp	Phe	Val 660	Gly	Ala	Leu	Ile	Phe 665	Ser	Gly	Ala	Val	Ile 670	Leu	Leu
Glu	Phe	Ile 675	Pro	Glu	Ile	Ala	Ile 680	Pro	Val	Leu	Gly	Thr 685	Phe	Ala	Leu
Val	Ser 690	Tyr	Ile	Ala	Asn 695	Lys	Val	Leu	Thr	Val 700	Gln	Thr	Ile	Asp	Asn
Ala 705	Leu	Ser	Lys	Arg	Asn 710	Glu	Lys	Trp	Asp	Glu 715	Val	Tyr	Lys	Tyr	Ile 720
Val	Thr	Asn	Trp	Leu 725	Ala	Lys	Val	Asn 730	Thr	Gln	Ile	Asp	Leu	Ile	Arg 735
Lys	Lys	Met	Lys 740	Glu	Ala	Leu	Glu	Asn 745	Gln	Ala	Glu	Ala	Thr 750	Lys	Ala
Ile	Ile	Asn	Tyr	Gln	Tyr	Asn 755	Gln	Tyr	Thr	Glu	Glu	Glu 765	Lys	Asn	Asn
Ile	Asn 770	Phe	Asn	Ile	Asp	Asp 775	Leu	Ser	Ser	Lys	Leu 780	Asn	Glu	Ser	Ile
Asn 785	Lys	Ala	Met	Ile	Asn 790	Ile	Asn	Lys	Phe	Leu 795	Asn	Gln	Cys	Ser	Val 800
Ser	Tyr	Leu	Met	Asn 805	Ser	Met	Ile	Pro	Tyr	Gly	Val	Lys	Arg	Leu	Glu 815

Asp	Phe	Asp	Ala 820	Ser	Leu	Lys	Asp	Ala 825	Leu	Leu	Lys	Tyr	Ile 830	Tyr	Asp
Asn	Arg	Gly 835	Thr	Leu	Ile	Gly	Gln 840	Val	Asp	Arg	Leu	Lys 845	Asp	Lys	Val
Asn	Asn 850	Thr	Leu	Ser	Thr	Asp 855	Ile	Pro	Phe	Gln	Leu 860	Ser	Lys	Tyr	Val
Asp 865	Asn	Gln	Arg	Leu	Leu 870	Ser	Thr	Phe	Thr	Glu 875	Tyr	Ile	Lys	Ser	Arg 880
Pro	Gly	Pro	Glu	Thr 885	Leu	Cys	Gly	Ala	Glu 890	Leu	Val	Asp	Ala	Leu 895	Gln
Phe	Val	Cys	Gly 900	Asp	Arg	Gly	Phe	Tyr 905	Phe	Asn	Lys	Pro	Thr 910	Gly	Tyr
Gly	Ser	Ser 915	Ser	Arg	Arg	Ala	Pro 920	Gln	Thr	Gly	Ile	Val 925	Asp	Glu	Cys
Cys	Phe 930	Arg	Ser	Cys	Asp	Leu 935	Arg	Arg	Leu	Glu	Met 940	Tyr	Cys	Ala	Pro
Leu 945	Lys	Pro	Ala	Lys	Ser 950	Ala	Glu	Ala	*						

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 2724 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

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(ix) FEATURE:
      (A) NAME/KEY: CDS
      (B) LOCATION: 1..2724
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ATG	CAG	TTC	GTG	AAC	AAG	CAG	TTC	AAC	TAT	AAG	GAC	CCT	GTA	AAC	GGT	48
Met	Gln	Phe	Val	Asn	Lys	Gln	Phe	Asn	Tyr	Lys	Asp	Pro	Val	Asn	Gly	
1				5					10					15		
GTT	GAC	ATT	GCC	TAC	ATC	AAA	ATT	CCA	AAC	GCC	GGC	CAG	ATG	CAG	CCG	96
Val	Asp	Ile	Ala	Tyr	Ile	Lys	Ile	Pro	Asn	Ala	Gly	Gln	Met	Gln	Pro	
			20					25					30			
GTG	AAG	GCT	TTC	AAG	ATT	CAT	AAC	AAA	ATC	TGG	GTT	ATT	CCG	GAA	CGC	144
Val	Lys	Ala	Phe	Lys	Ile	His	Asn	Lys	Ile	Trp	Val	Ile	Pro	Glu	Arg	
		35					40					45				
GAT	ACA	TTT	ACG	AAC	CCG	GAA	GAA	GGA	GAC	TTG	AAC	CCG	CCG	CCG	GAA	192
Asp	Thr	Phe	Thr	Asn	Pro	Glu	Glu	Gly	Asp	Leu	Asn	Pro	Pro	Pro	Glu	
	50					55					60					
GCA	AAG	CAG	GTG	CCA	GTT	TCA	TAC	TAC	GAT	TCA	ACC	TAT	CTG	AGC	ACA	240
Ala	Lys	Gln	Val	Pro	Val	Ser	Tyr	Tyr	Asp	Ser	Thr	Tyr	Leu	Ser	Thr	
65				70					75						80	
GAC	AAC	GAG	AAG	GAT	AAC	TAC	CTG	AAG	GGA	GTG	ACC	AAA	TTA	TTC	GAG	288
Asp	Asn	Glu	Lys	Asp	Asn	Tyr	Leu	Lys	Gly	Val	Thr	Lys	Leu	Phe	Glu	
				85					90					95		

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CGT	ATT	TAT	TCC	ACT	GAC	CTG	GGC	CGT	ATG	CTG	CTG	ACC	TCA	ATC	GTC	336
Arg	Ile	Tyr	Ser	Thr	Asp	Leu	Gly	Arg	Met	Leu	Leu	Thr	Ser	Ile	Val	
			100					105					110			
CGC	GGA	ATC	CCA	TTT	TGG	GGT	GGC	AGT	ACC	ATT	GAC	ACG	GAG	TTG	AAG	384
Arg	Gly	Ile	Pro	Phe	Trp	Gly	Gly	Ser	Thr	Ile	Asp	Thr	Glu	Leu	Lys	
		115					120					125				
GTT	ATT	GAC	ACT	AAC	TGC	ATT	AAC	GTG	ATC	CAA	CCA	GAC	GGT	AGC	TAC	432
Val	Ile	Asp	Thr	Asn	Cys	Ile	Asn	Val	Ile	Gln	Pro	Asp	Gly	Ser	Tyr	
	130					135					140					
AGA	TCT	GAA	GAA	CTT	AAC	CTC	GTA	ATC	ATC	GGG	CCC	TCC	GCG	GAC	ATT	480
Arg	Ser	Glu	Glu	Leu	Asn	Leu	Val	Ile	Ile	Gly	Pro	Ser	Ala	Asp	Ile	
145					150					155					160	
ATC	CAG	TTT	GAG	TGC	AAG	AGC	TTT	GGC	CAC	GAA	GTG	TTG	AAC	CTG	ACG	528
Ile	Gln	Phe	Glu	Cys	Lys	Ser	Phe	Gly	His	Glu	Val	Leu	Asn	Leu	Thr	
				165					170					175		
CGT	AAC	GGT	TAC	GGC	TCT	ACT	CAG	TAC	ATT	CGT	TTC	AGC	CCA	GAC	TTC	576
Arg	Asn	Gly	Tyr	Gly	Ser	Thr	Gln	Tyr	Ile	Arg	Phe	Ser	Pro	Asp	Phe	
			180					185					190			
ACG	TTC	GGT	TTC	GAG	GAG	AGC	CTG	GAG	GTT	GAT	ACC	AAC	CCG	CTG	TTG	624
Thr	Phe	Gly	Phe	Glu	Glu	Ser	Leu	Glu	Val	Asp	Thr	Asn	Pro	Leu	Leu	
		195					200					205				
GGT	GCA	GGC	AAG	TTC	GCA	ACT	GAT	CCA	GCG	GTG	ACC	CTG	GCA	CAC	GAG	672
Gly	Ala	Gly	Lys	Phe	Ala	Thr	Asp	Pro	Ala	Val	Thr	Leu	Ala	His	Glu	
	210					215					220					
CTG	ATC	CAC	GCC	GGT	CAT	CGT	CTG	TAT	GGC	ATT	GCG	ATT	AAC	CCG	AAC	720
Leu	Ile	His	Ala	Gly	His	Arg	Leu	Tyr	Gly	Ile	Ala	Ile	Asn	Pro	Asn	
225					230					235					240	
CGC	GTG	TTC	AAG	GTT	AAC	ACC	AAC	GCC	TAC	TAC	GAG	ATG	AGT	GGT	TTA	768
Arg	Val	Phe	Lys	Val	Asn	Thr	Asn	Ala	Tyr	Tyr	Glu	Met	Ser	Gly	Leu	
				245					250					255		
GAA	GTA	AGC	TTC	GAG	GAA	CTG	CGC	ACG	TTC	GGT	GGC	CAT	GAT	GCG	AAG	816
Glu	Val	Ser	Phe	Glu	Glu	Leu	Arg	Thr	Phe	Gly	Gly	His	Asp	Ala	Lys	
			260					265					270			
TTT	ATC	GAC	AGC	TTG	CAG	GAG	AAC	GAG	TTC	CGT	CTG	TAC	TAC	TAC	AAC	864
Phe	Ile	Asp	Ser	Leu	Gln	Glu	Asn	Glu	Phe	Arg	Leu	Tyr	Tyr	Tyr	Asn	
		275					280					285				
AAG	TTT	AAA	GAT	ATT	GCA	AGT	ACA	CTG	AAC	AAG	GCT	AAG	TCC	ATT	GTG	912
Lys	Phe	Lys	Asp	Ile	Ala	Ser	Thr	Leu	Asn	Lys	Ala	Lys	Ser	Ile	Val	
	290					295					300					
GGT	ACC	ACT	GCT	TCA	TTA	CAG	TAT	ATG	AAA	AAT	GTT	TTT	AAA	GAG	AAA	960
Gly	Thr	Thr	Ala	Ser	Leu	Gln	Tyr	Met	Lys	Asn	Val	Phe	Lys	Glu	Lys	
305					310					315				320		
TAT	CTC	CTA	TCT	GAA	GAT	ACA	TCT	GGA	AAA	TTT	TCG	GTA	GAT	AAA	TTA	1008
Tyr	Leu	Leu	Ser	Glu	Asp	Thr	Ser	Gly	Lys	Phe	Ser	Val	Asp	Lys	Leu	
				325					330					335		
AAA	TTT	GAT	AAG	TTA	TAC	AAA	ATG	TTA	ACA	GAG	ATT	TAC	ACA	GAG	GAT	1056
Lys	Phe	Asp	Lys	Leu	Tyr	Lys	Met	Leu	Thr	Glu	Ile	Tyr	Thr	Glu	Asp	
			340					345					350			
AAT	TTT	GTT	AAG	TTT	TTT	AAA	GTA	CTT	AAC	AGA	AAA	ACA	TAT	TTG	AAT	1104
Asn	Phe	Val	Lys	Phe	Phe	Lys	Val	Leu	Asn	Arg	Lys	Thr	Tyr	Leu	Asn	
		355					360					365				

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TTT GAT AAA GCC GTA TTT AAG ATA AAT ATA GTA CCT AAG GTA AAT TAC	1152
Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val Asn Tyr	
370 375 380	
ACA ATA TAT GAT GGA TTT AAT TTA AGA AAT ACA AAT TTA GCA GCA AAC	1200
Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala Ala Asn	
385 390 395 400	
TTT AAT GGT CAA AAT ACA GAA ATT AAT AAT ATG AAT TTT ACT AAA CTA	1248
Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr Lys Leu	
405 410 415	
AAA AAT TTT ACT GGA TTG TTT GAA TTT TAT AAG TTG CTA TGT GTA AGA	1296
Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys Val Arg	
420 425 430	
GGG ATA ATA ACT TCT AAA ACT AAA TCA TTA GAT AAA GGA TAC AAT AAG	1344
Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Asp Lys Gly Tyr Asn Lys	
435 440 445	
ATC GAA GGT CGT TGC GAT GGG GCA TTA AAT GAT TTA TGT ATC AAA GTT	1392
Ile Glu Gly Arg Cys Asp Gly Ala Leu Asn Asp Leu Cys Ile Lys Val	
450 455 460	
AAT AAT TGG GAC TTG TTT TTT AGT CCT TCA GAA GAT AAT TTT ACT AAT	1440
Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn	
465 470 475 480	
GAT CTA AAT AAA GGA GAA GAA ATT ACA TCT GAT ACT AAT ATA GAA GCA	1488
Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala	
485 490 495	
GCA GAA GAA AAT ATT AGT TTA GAT TTA ATA CAA CAA TAT TAT TTA ACC	1536
Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr	
500 505 510	
TTT AAT TTT GAT AAT GAA CCT GAA AAT ATT TCA ATA GAA AAT CTT TCA	1584
Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser	
515 520 525	
AGT GAC ATT ATA GGC CAA TTA GAA CTT ATG CCT AAT ATA GAA AGA TTT	1632
Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe	
530 535 540	
CCT AAT GGA AAA AAG TAT GAG TTA GAT AAA TAT ACT ATG TTC CAT TAT	1680
Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr	
545 550 555 560	
CTT CGT GCT CAA GAA TTT GAA CAT GGT AAA TCT AGG ATT GCT TTA ACA	1728
Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr	
565 570 575	
AAT TCT GTT AAC GAA GCA TTA TTA AAT CCT AGT CGT GTT TAT ACA TTT	1776
Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe	
580 585 590	
TTT TCT TCA GAC TAT GTA AAG AAA GTT AAT AAA GCT ACG GAG GCA GCT	1824
Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala	
595 600 605	
ATG TTT TTA GGC TGG GTA GAA CAA TTA GTA TAT GAT TTT ACC GAT GAA	1872
Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu	
610 615 620	
ACT AGC GAA GTA AGT ACT ACG GAT AAA ATT GCG GAT ATA ACT ATA ATT	1920
Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile	
625 630 635 640	

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ATT CCA TAT ATA GGA CCT GCT TTA AAT ATA GGT AAT ATG TTA TAT AAA Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys 645 650 655	1968
GAT GAT TTT GTA GGT GCT TTA ATA TTT TCA GGA GCT GTT ATT CTG TTA Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu 660 665 670	2016
GAA TTT ATA CCA GAG ATT GCA ATA CCT GTA TTA GGT ACT TTT GCA CTT Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu 675 680 685	2064
GTA TCA TAT ATT GCG AAT AAG GTT CTA ACC GTT CAA ACA ATA GAT AAT Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn 690 695 700	2112
GCT TTA AGT AAA AGA AAT GAA AAA TGG GAT GAG GTC TAT AAA TAT ATA Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile 705 710 715 720	2160
GTA ACA AAT TGG TTA GCA AAG GTT AAT ACA CAG ATT GAT CTA ATA AGA Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg 725 730 735	2208
AAA AAA ATG AAA GAA GCT TTA GAA AAT CAA GCA GAA GCA ACA AAG GCT Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala 740 745 750	2256
ATA ATA AAC TAT CAG TAT AAT CAA TAT ACT GAG GAA GAG AAA AAT AAT Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn 755 760 765	2304
ATT AAT TTT AAT ATT GAT GAT TTA AGT TCG AAA CTT AAT GAG TCT ATA Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile 770 775 780	2352
AAT AAA GCT ATG ATT AAT ATA AAT AAA TTT TTG AAT CAA TGC TCT GTT Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val 785 790 795 800	2400
TCA TAT TTA ATG AAT TCT ATG ATC CCT TAT GGT GTT AAA CGG TTA GAA Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu 805 810 815	2448
GAT TTT GAT GCT AGT CTT AAA GAT GCA TTA TTA AAG TAT ATA TAT GAT Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp 820 825 830	2496
AAT AGA GGA ACT TTA ATT GGT CAA GTA GAT AGA TTA AAA GAT AAA GTT Asn Arg Gly Thr Leu Ile Gly Glu Val Asp Arg Leu Lys Asp Lys Val 835 840 845	2544
AAT AAT ACA CTT AGT ACA GAT ATA CCT TTT CAG CTT TCC AAA TAC GTA Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val 850 855 860	2592
GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TCT AGG Asp Asn Gln Arg Leu Leu Ser Thr Phe Thr Glu Tyr Ile Lys Ser Arg 865 870 875 880	2640
CCT CAA TCT AAA GTT AAA AGA CAA ATA TTT TCA GGC TAT CAA TCT GAT Pro Gln Ser Lys Val Lys Arg Gln Ile Phe Ser Gly Tyr Gln Ser Asp 885 890 895	2688
<del>ATT GAT ACA GAT AAT AGA ATT AAG GAT GAA TTA TGA</del> <del>Ile Asp Thr His Asn Arg Ile Lys Asp Glu Leu *</del> 900 905	<del>2724</del>

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## (2) INFORMATION FOR SEQ ID NO: 16:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 908 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

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Met Gln Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly
 1           5           10           15
Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro
          20           25           30
Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg
          35           40           45
Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro Pro Glu
          50           55           60
Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr
          65           70           75           80
Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu
          85           90           95
Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val
          100          105          110
Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys
          115          120          125
Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr
          130          135          140
Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile
          145          150          155          160
Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr
          165          170          175
Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe
          180          185          190
Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu
          195          200          205
Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu
          210          215          220
Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn
          225          230          235          240
Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu
          245          250          255
Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys
          260          265          270
Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn
          275          280          285
Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser Ile Val
          290          295          300

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Gly	Thr	Thr	Ala	Ser	Leu	Gln	Tyr	Met	Lys	Asn	Val	Phe	Lys	Glu	Lys	305	310	315	320
Tyr	Leu	Leu	Ser	Glu	Asp	Thr	Ser	Gly	Lys	Phe	Ser	Val	Asp	Lys	Leu	325	330	335	
Lys	Phe	Asp	Lys	Leu	Tyr	Lys	Met	Leu	Thr	Glu	Ile	Tyr	Thr	Glu	Asp	340	345	350	
Asn	Phe	Val	Lys	Phe	Phe	Lys	Val	Leu	Asn	Arg	Lys	Thr	Tyr	Leu	Asn	355	360	365	
Phe	Asp	Lys	Ala	Val	Phe	Lys	Ile	Asn	Ile	Val	Pro	Lys	Val	Asn	Tyr	370	375	380	
Thr	Ile	Tyr	Asp	Gly	Phe	Asn	Leu	Arg	Asn	Thr	Asn	Leu	Ala	Ala	Asn	385	390	395	400
Phe	Asn	Gly	Gln	Asn	Thr	Glu	Ile	Asn	Asn	Met	Asn	Phe	Thr	Lys	Leu	405	410	415	
Lys	Asn	Phe	Thr	Gly	Leu	Phe	Glu	Phe	Tyr	Lys	Leu	Leu	Cys	Val	Arg	420	425	430	
Gly	Ile	Ile	Thr	Ser	Lys	Thr	Lys	Ser	Leu	Asp	Lys	Gly	Tyr	Asn	Lys	435	440	445	
Ile	Glu	Gly	Arg	Cys	Asp	Gly	Ala	Leu	Asn	Asp	Leu	Cys	Ile	Lys	Val	450	455	460	
Asn	Asn	Trp	Asp	Leu	Phe	Phe	Ser	Pro	Ser	Glu	Asp	Asn	Phe	Thr	Asn	465	470	475	480
Asp	Leu	Asn	Lys	Gly	Glu	Glu	Ile	Thr	Ser	Asp	Thr	Asn	Ile	Glu	Ala	485	490	495	
Ala	Glu	Glu	Asn	Ile	Ser	Leu	Asp	Leu	Ile	Gln	Gln	Tyr	Tyr	Leu	Thr	500	505	510	
Phe	Asn	Phe	Asp	Asn	Glu	Pro	Glu	Asn	Ile	Ser	Ile	Glu	Asn	Leu	Ser	515	520	525	
Ser	Asp	Ile	Ile	Gly	Gln	Leu	Glu	Leu	Met	Pro	Asn	Ile	Glu	Arg	Phe	530	535	540	
Pro	Asn	Gly	Lys	Lys	Tyr	Glu	Leu	Asp	Lys	Tyr	Thr	Met	Phe	His	Tyr	545	550	555	560
Leu	Arg	Ala	Gln	Glu	Phe	Glu	His	Gly	Lys	Ser	Arg	Ile	Ala	Leu	Thr	565	570	575	
Asn	Ser	Val	Asn	Glu	Ala	Leu	Leu	Asn	Pro	Ser	Arg	Val	Tyr	Thr	Phe	580	585	590	
Phe	Ser	Ser	Asp	Tyr	Val	Lys	Lys	Val	Asn	Lys	Ala	Thr	Glu	Ala	Ala	595	600	605	
Met	Phe	Leu	Gly	Trp	Val	Glu	Gln	Leu	Val	Tyr	Asp	Phe	Thr	Asp	Glu	610	615	620	
Thr	Ser	Glu	Val	Ser	Thr	Thr	Asp	Lys	Ile	Ala	Asp	Ile	Thr	Ile	Ile	625	630	635	640
Ile	Pro	Tyr	Ile	Gly	Pro	Ala	Leu	Asn	Ile	Gly	Asn	Met	Leu	Tyr	Lys	645	650	655	



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Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu  
 660 665 670  
 Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu  
 675 680 685  
 Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn  
 690 695 700  
 Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile  
 705 710 715 720  
 Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg  
 725 730 735  
 Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala  
 740 745 750  
 Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn  
 755 760 765  
 Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile  
 770 775 780  
 Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val  
 785 790 795 800  
 Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu  
 805 810 815  
 Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp  
 820 825 830  
 Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val  
 835 840 845  
 Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val  
 850 855 860  
 Asp Asn Gln Arg Leu Leu Ser Thr Phe Thr Glu Tyr Ile Lys Ser Arg  
 865 870 875 880  
 Pro Gln Ser Lys Val Lys Arg Gln Ile Phe Ser Gly Tyr Gln Ser Asp  
 885 890 895  
 Ile Asp Thr His Asn Arg Ile Lys Asp Glu Leu \*  
 900 905

## (2) INFORMATION FOR SEQ ID NO: 17:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3042 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..3042

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

ATG CAG TTC GTG AAC AAG CAG TTC AAC TAT AAG GAC CCT GTA AAC GGT 48  
 Met Gln Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly  
 1 5 10 15

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GTT GAC ATT GCC TAC ATC AAA ATT CCA AAC GCC GGC CAG ATG CAG CCG Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro 20 25 30	96
GTG AAG GCT TTC AAG ATT CAT AAC AAA ATC TGG GTT ATT CCG GAA CGC Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg 35 40 45	144
GAT ACA TTT ACG AAC CCG GAA GAA GGA GAC TTG AAC CCG CCG CCG GAA Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro Pro Glu 50 55 60	192
GCA AAG CAG GTG CCA GTT TCA TAC TAC GAT TCA ACC TAT CTG AGC ACA Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr 65 70 75 80	240
GAC AAC GAG AAG GAT AAC TAC CTG AAG GGA GTG ACC AAA TTA TTC GAG Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu 85 90 95	288
CGT ATT TAT TCC ACT GAC CTG GGC CGT ATG CTG CTG ACC TCA ATC GTC Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val 100 105 110	336
CGC GGA ATC CCA TTT TGG GGT GGC AGT ACC ATT GAC ACG GAG TTG AAG Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys 115 120 125	384
GTT ATT GAC ACT AAC TGC ATT AAC GTG ATC CAA CCA GAC GGT AGC TAC Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr 130 135 140	432
AGA TCT GAA GAA CTT AAC CTC GTA ATC ATC GGG CCC TCC GCG GAC ATT Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile 145 150 155 160	480
ATC CAG TTT GAG TGC AAG AGC TTT GGC CAC GAA GTG TTG AAC CTG ACG Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr 165 170 175	528
CGT AAC GGT TAC GGC TCT ACT CAG TAC ATT CGT TTC AGC CCA GAC TTC Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe 180 185 190	576
ACG TTC GGT TTC GAG GAG AGC CTG GAG GTT GAT ACC AAC CCG CTG TTG Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu 195 200 205	624
GGT GCA GGC AAG TTC GCA ACT GAT CCA GCG GTG ACC CTG GCA CAC GAG Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu 210 215 220	672
CTG ATC CAC GCC GGT CAT CGT CTG TAT GGC ATT GCG ATT AAC CCG AAC Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn 225 230 235 240	720
CGC GTG TTC AAG GTT AAC ACC AAC GCC TAC TAC GAG ATG AGT GGT TTA Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu 245 250 255	768
GAA GTA AGC TTC GAG GAA CTG CGC ACG TTC GGT GGC CAT GAT GCG AAG Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys 260 265 270	816
TTT ATC GAC AGC TTG CAG GAG AAC GAG TTC CGT CTG TAC TAC TAC AAC Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn 275 280 285	864

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AAG Lys 290	TTT Phe 290	AAA Lys 290	GAT Asp 290	ATT Ile 290	GCA Ala 295	AGT Ser 295	ACA Thr 295	CTG Leu 295	AAC Asn 300	AAG Lys 300	GCT Ala 300	AAG Lys 300	TCC Ser 300	ATT Ile 300	GTG Val 300	912
GGT Gly 305	ACC Thr 305	ACT Thr 305	GCT Ala 305	TCA Ser 310	TTA Leu 310	CAG Gln 310	TAT Tyr 310	ATG Met 315	AAA Lys 315	AAT Asn 315	GTT Val 315	TTT Phe 315	AAA Lys 315	GAG Glu 320	AAA Lys 320	960
TAT Tyr 325	CTC Leu 325	CTA Leu 325	TCT Ser 325	GAA Glu 325	GAT Asp 325	ACA Thr 325	TCT Ser 330	GGA Gly 330	AAA Lys 330	TTT Phe 330	TCG Ser 330	GTA Val 335	GAT Asp 335	AAA Lys 335	TTA Leu 335	1008
AAA Lys 340	TTT Phe 340	GAT Asp 340	AAG Lys 340	TTA Leu 340	TAC Tyr 340	AAA Lys 345	ATG Met 345	TTA Leu 345	ACA Thr 345	GAG Glu 350	ATT Ile 350	TAC Tyr 350	ACA Thr 350	GAG Glu 350	GAT Asp 350	1056
AAT Asn 355	TTT Phe 355	GTT Val 355	AAG Lys 355	TTT Phe 355	TTT Phe 355	AAA Lys 360	GTA Val 360	CTT Leu 360	AAC Asn 360	AGA Arg 365	AAA Lys 365	ACA Thr 365	TAT Tyr 365	TTG Leu 365	AAT Asn 365	1104
TTT Phe 370	GAT Asp 370	AAA Lys 370	GCC Ala 370	GTA Val 370	TTT Phe 375	AAG Lys 375	ATA Ile 375	AAT Asn 375	ATA Ile 375	GTA Val 380	CCT Pro 380	AAG Lys 380	GTA Val 380	AAT Asn 380	TAC Tyr 380	1152
ACA Thr 385	ATA Ile 385	TAT Tyr 385	GAT Asp 385	GGA Gly 390	TTT Phe 390	AAT Asn 390	TTA Leu 390	AGA Arg 395	AAT Asn 395	ACA Thr 395	AAT Asn 395	TTA Leu 395	GCA Ala 400	GCA Ala 400	AAC Asn 400	1200
TTT Phe 405	AAT Asn 405	GGT Gly 405	CAA Gln 405	AAT Asn 405	ACA Thr 405	GAA Glu 410	ATT Ile 410	AAT Asn 410	AAT Asn 410	ATG Met 415	AAT Asn 415	TTT Phe 415	ACT Thr 415	AAA Lys 415	CTA Leu 415	1248
AAA Lys 420	AAT Asn 420	TTT Phe 420	ACT Thr 420	GGA Gly 425	TTG Leu 425	TTT Phe 425	GAA Glu 425	TTT Phe 425	TAT Tyr 430	AAG Lys 430	TTG Leu 430	CTA Leu 430	TGT Cys 430	GTA Val 430	AGA Arg 430	1296
GGG Gly 435	ATA Ile 435	ATA Ile 435	ACT Thr 435	TCT Ser 440	AAA Lys 440	ACT Thr 440	AAA Lys 440	TCA Ser 445	TTA Leu 445	GAT Asp 445	AAA Lys 445	GGA Gly 445	TAC Tyr 445	AAT Asn 445	AAG Lys 445	1344
ATC Ile 450	GAA Glu 450	GGT Gly 450	CGT Arg 450	TGC Cys 455	GAT Asp 455	GGG Gly 455	GCA Ala 455	TTA Leu 455	AAT Asn 460	GAT Asp 460	TTA Leu 460	TGT Cys 460	ATC Ile 460	AAA Lys 460	GTT Val 460	1392
AAT Asn 465	AAT Asn 465	TGG Trp 465	GAC Asp 465	TTG Leu 470	TTT Phe 470	TTT Phe 470	AGT Ser 475	CCT Pro 475	TCA Ser 475	GAA Glu 475	GAT Asp 475	AAT Asn 475	TTT Phe 475	ACT Thr 480	AAT Asn 480	1440
GAT Asp 485	CTA Leu 485	AAT Asn 485	AAA Lys 485	GGA Gly 485	GAA Glu 490	GAA Glu 490	ATT Ile 490	ACA Thr 490	TCT Ser 490	GAT Asp 495	ACT Thr 495	AAT Asn 495	ATA Ile 495	GAA Glu 495	GCA Ala 495	1488
GCA Ala 500	GAA Glu 500	GAA Glu 500	AAT Asn 500	ATT Ile 500	AGT Ser 505	TTA Leu 505	GAT Asp 505	TTA Leu 505	ATA Ile 505	CAA Gln 510	CAA Gln 510	TAT Tyr 510	TAT Tyr 510	TTA Leu 510	ACC Thr 510	1536
TTT Phe 515	AAT Asn 515	TTT Phe 515	GAT Asp 515	AAT Asn 515	GAA Glu 520	CCT Pro 520	GAA Glu 520	AAT Asn 520	ATT Ile 525	TCA Ser 525	ATA Ile 525	GAA Glu 525	AAT Asn 525	CTT Leu 525	TCA Ser 525	1584
AGT Ser 530	GAC Ile 530	ATT Ile 530	ATA Ile 530	GGC Gly 535	CAA Gln 535	TTA Leu 535	GAA Glu 535	CTT Leu 540	ATG Met 540	CCT Pro 540	AAT Asn 540	ATA Ile 540	GAA Glu 540	AGA Arg 540	TTT Phe 540	1632
CCT Pro 545	AAT Asn 545	GGA Gly 545	AAA Lys 545	AAG Lys 545	TAT Tyr 550	GAG Glu 550	TTA Leu 550	GAT Asp 555	AAA Lys 555	TAT Tyr 555	ACT Thr 555	ATG Met 555	TTC Phe 555	CAT His 555	TAT Tyr 560	1680

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CTT	CGT	GCT	CAA	GAA	TTT	GAA	CAT	GGT	AAA	TCT	AGG	ATT	GCT	TTA	ACA	1728
Leu	Arg	Ala	Gln	Glu	Phe	Glu	His	Gly	Lys	Ser	Arg	Ile	Ala	Leu	Thr	
			565						570						575	
AAT	TCT	GTT	AAC	GAA	GCA	TTA	TTA	AAT	CCT	AGT	CGT	GTT	TAT	ACA	TTT	1776
Asn	Ser	Val	Asn	Glu	Ala	Leu	Leu	Asn	Pro	Ser	Arg	Val	Tyr	Thr	Phe	
			580					585					590			
TTT	TCT	TCA	GAC	TAT	GTA	AAG	AAA	GTT	AAT	AAA	GCT	ACG	GAG	GCA	GCT	1824
Phe	Ser	Ser	Asp	Tyr	Val	Lys	Lys	Val	Asn	Lys	Ala	Thr	Glu	Ala	Ala	
		595					600					605				
ATG	TTT	TTA	GGC	TGG	GTA	GAA	CAA	TTA	GTA	TAT	GAT	TTT	ACC	GAT	GAA	1872
Met	Phe	Leu	Gly	Trp	Val	Glu	Gln	Leu	Val	Tyr	Asp	Phe	Thr	Asp	Glu	
	610					615					620					
ACT	AGC	GAA	GTA	AGT	ACT	ACG	GAT	AAA	ATT	GCG	GAT	ATA	ACT	ATA	ATT	1920
Thr	Ser	Glu	Val	Ser	Thr	Thr	Asp	Lys	Ile	Ala	Asp	Ile	Thr	Ile	Ile	
	625				630					635					640	
ATT	CCA	TAT	ATA	GGA	CCT	GCT	TTA	AAT	ATA	GGT	AAT	ATG	TTA	TAT	AAA	1968
Ile	Pro	Tyr	Ile	Gly	Pro	Ala	Leu	Asn	Ile	Gly	Asn	Met	Leu	Tyr	Lys	
			645					650							655	
GAT	GAT	TTT	GTA	GGT	GCT	TTA	ATA	TTT	TCA	GGA	GCT	GTT	ATT	CTG	TTA	2016
Asp	Asp	Phe	Val	Gly	Ala	Leu	Ile	Phe	Ser	Gly	Ala	Val	Ile	Leu	Leu	
		660					665						670			
GAA	TTT	ATA	CCA	GAG	ATT	GCA	ATA	CCT	GTA	TTA	GGT	ACT	TTT	GCA	CTT	2064
Glu	Phe	Ile	Pro	Glu	Ile	Ala	Ile	Pro	Val	Leu	Gly	Thr	Phe	Ala	Leu	
		675					680					685				
GTA	TCA	TAT	ATT	GCG	AAT	AAG	GTT	CTA	ACC	GTT	CAA	ACA	ATA	GAT	AAT	2112
Val	Ser	Tyr	Ile	Ala	Asn	Lys	Val	Leu	Thr	Val	Gln	Thr	Ile	Asp	Asn	
	690					695					700					
GCT	TTA	AGT	AAA	AGA	AAT	GAA	AAA	TGG	GAT	GAG	GTC	TAT	AAA	TAT	ATA	2160
Ala	Leu	Ser	Lys	Arg	Asn	Glu	Lys	Trp	Asp	Glu	Val	Tyr	Lys	Tyr	Ile	
	705				710					715					720	
GTA	ACA	AAT	TGG	TTA	GCA	AAG	GTT	AAT	ACA	CAG	ATT	GAT	CTA	ATA	AGA	2208
Val	Thr	Asn	Trp	Leu	Ala	Lys	Val	Asn	Thr	Gln	Ile	Asp	Leu	Ile	Arg	
			725						730					735		
AAA	AAA	ATG	AAA	GAA	GCT	TTA	GAA	AAT	CAA	GCA	GAA	GCA	ACA	AAG	GCT	2256
Lys	Lys	Met	Lys	Glu	Ala	Leu	Glu	Asn	Gln	Ala	Glu	Ala	Thr	Lys	Ala	
			740					745					750			
ATA	ATA	AAC	TAT	CAG	TAT	AAT	CAA	TAT	ACT	GAG	GAA	GAG	AAA	AAT	AAT	2304
Ile	Ile	Asn	Tyr	Gln	Tyr	Asn	Gln	Tyr	Thr	Glu	Glu	Glu	Lys	Asn	Asn	
		755					760					765				
ATT	AAT	TTT	AAT	ATT	GAT	GAT	TTA	AGT	TCG	AAA	CTT	AAT	GAG	TCT	ATA	2352
Ile	Asn	Phe	Asn	Ile	Asp	Asp	Leu	Ser	Ser	Lys	Leu	Asn	Glu	Ser	Ile	
	770					775						780				
AAT	AAA	GCT	ATG	ATT	AAT	ATA	AAT	AAA	TTT	TTG	AAT	CAA	TGC	TCT	GTT	2400
Asn	Lys	Ala	Met	Ile	Asn	Ile	Asn	Lys	Phe	Leu	Asn	Gln	Cys	Ser	Val	
	785				790					795					800	
TCA	TAT	TTA	ATG	AAT	TCT	ATG	ATC	CCT	TAT	GGT	GTT	AAA	CGG	TTA	GAA	2448
Ser	Tyr	Leu	Met	Asn	Ser	Met	Ile	Pro	Tyr	Gly	Val	Lys	Arg	Leu	Glu	
				805					810						815	
GAT	TTT	GAT	GCT	AGT	CTT	AAA	GAT	GCA	TTA	TTA	AAG	TAT	ATA	TAT	GAT	2496
Asp	Phe	Asp	Ala	Ser	Leu	Lys	Asp	Ala	Leu	Leu	Lys	Tyr	Ile	Tyr	Asp	
			820					825					830			

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AAT AGA GGA ACT TTA ATT GGT CAA GTA GAT AGA TTA AAA GAT AAA GTT Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val 835 840 845	2544
AAT AAT ACA CTT AGT ACA GAT ATA CCT TTT CAG CTT TCC AAA TAC GTA Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val 850 855 860	2592
GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TCA GGC Asp Asn Gln Arg Leu Leu Ser Thr Phe Thr Glu Tyr Ile Lys Ser Gly 865 870 875 880	2640
CTG AAT TCC CCG GGT GCA GCT CAT TAT GCG CAA CAC GAT GAA GCC GTA Leu Asn Ser Pro Gly Ala Ala His Tyr Ala Gln His Asp Glu Ala Val 885 890 895	2688
GAC AAC AAA TTC AAC AAA GAA CAA CAA AAC GCG TTC TAT GAG ATC TTA Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu 900 905 910	2736
CAT TTA CCT AAC TTA AAC GAA GAA CAA CGA AAC GCC TTC ATC CAA AGT His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn Ala Phe Ile Gln Ser 915 920 925	2784
TTA AAA GAT GAC CCA AGC CAA AGC GCT AAC CTT TTA GCA GAA GCT AAA Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Leu Leu Ala Glu Ala Lys 930 935 940	2832
AAG CTA AAT GAT GCT CAG GCG CCG AAA GTA GAC AAC AAA TTC AAC AAA Lys Leu Asn Asp Ala Gln Ala Pro Lys Val Asp Asn Lys Phe Asn Lys 945 950 955 960	2880
GAA CAA CAA AAC GCG TTC TAT GAG ATC TTA CAT TTA CCT AAC TTA AAC Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu His Leu Pro Asn Leu Asn 965 970 975	2928
GAA GAA CAA CGA AAC GCC TTC ATC CAA AGT TTA AAA GAT GAC CCA AGC Glu Glu Gln Arg Asn Ala Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser 980 985 990	2976
CAA AGC GCT AAC CTT TTA GCA GAA GCT AAA AAG CTA AAT GAT GCT CAG Gln Ser Ala Asn Leu Leu Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln 995 1000 1005	3024
GCG CCG AAA GTA GAC TAG Ala Pro Lys Val Asp *	3042
1010	

## (2) INFORMATION FOR SEQ ID NO: 18:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1014 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Met	Gln	Phe	Val	Asn	Lys	Gln	Phe	Asn	Tyr	Lys	Asp	Pro	Val	Asn	Gly
1				5					10					15	
Val	Asp	Ile	Ala	Tyr	Ile	Lys	Ile	Pro	Asn	Ala	Gly	Gln	Met	Gln	Pro
		20						25					30		
Val	Lys	Ala	Phe	Lys	Ile	His	Asn	Lys	Ile	Trp	Val	Ile	Pro	Glu	Arg
		35					40					45			

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Asp	Thr	Phe	Thr	Asn	Pro	Glu	Glu	Gly	Asp	Leu	Asn	Pro	Pro	Pro	Glu
50						55					60				
Ala	Lys	Gln	Val	Pro	Val	Ser	Tyr	Tyr	Asp	Ser	Thr	Tyr	Leu	Ser	Thr
65					70					75					80
Asp	Asn	Glu	Lys	Asp	Asn	Tyr	Leu	Lys	Gly	Val	Thr	Lys	Leu	Phe	Glu
				85					90					95	
Arg	Ile	Tyr	Ser	Thr	Asp	Leu	Gly	Arg	Met	Leu	Leu	Thr	Ser	Ile	Val
			100					105					110		
Arg	Gly	Ile	Pro	Phe	Trp	Gly	Gly	Ser	Thr	Ile	Asp	Thr	Glu	Leu	Lys
		115					120					125			
Val	Ile	Asp	Thr	Asn	Cys	Ile	Asn	Val	Ile	Gln	Pro	Asp	Gly	Ser	Tyr
130						135					140				
Arg	Ser	Glu	Glu	Leu	Asn	Leu	Val	Ile	Ile	Gly	Pro	Ser	Ala	Asp	Ile
145					150					155					160
Ile	Gln	Phe	Glu	Cys	Lys	Ser	Phe	Gly	His	Glu	Val	Leu	Asn	Leu	Thr
				165					170					175	
Arg	Asn	Gly	Tyr	Gly	Ser	Thr	Gln	Tyr	Ile	Arg	Phe	Ser	Pro	Asp	Phe
			180					185					190		
Thr	Phe	Gly	Phe	Glu	Glu	Ser	Leu	Glu	Val	Asp	Thr	Asn	Pro	Leu	Leu
		195					200					205			
Gly	Ala	Gly	Lys	Phe	Ala	Thr	Asp	Pro	Ala	Val	Thr	Leu	Ala	His	Glu
210						215					220				
Leu	Ile	His	Ala	Gly	His	Arg	Leu	Tyr	Gly	Ile	Ala	Ile	Asn	Pro	Asn
225					230					235					240
Arg	Val	Phe	Lys	Val	Asn	Thr	Asn	Ala	Tyr	Tyr	Glu	Met	Ser	Gly	Leu
				245					250					255	
Glu	Val	Ser	Phe	Glu	Glu	Leu	Arg	Thr	Phe	Gly	Gly	His	Asp	Ala	Lys
			260					265					270		
Phe	Ile	Asp	Ser	Leu	Gln	Glu	Asn	Glu	Phe	Arg	Leu	Tyr	Tyr	Tyr	Asn
		275					280					285			
Lys	Phe	Lys	Asp	Ile	Ala	Ser	Thr	Leu	Asn	Lys	Ala	Lys	Ser	Ile	Val
290						295					300				
Gly	Thr	Thr	Ala	Ser	Leu	Gln	Tyr	Met	Lys	Asn	Val	Phe	Lys	Glu	Lys
305					310					315				320	
Tyr	Leu	Leu	Ser	Glu	Asp	Thr	Ser	Gly	Lys	Phe	Ser	Val	Asp	Lys	Leu
				325					330					335	
Lys	Phe	Asp	Lys	Leu	Tyr	Lys	Met	Leu	Thr	Glu	Ile	Tyr	Thr	Glu	Asp
			340					345					350		
Asn	Phe	Val	Lys	Phe	Phe	Lys	Val	Leu	Asn	Arg	Lys	Thr	Tyr	Leu	Asn
		355					360					365			
Phe	Asp	Lys	Ala	Val	Phe	Lys	Ile	Asn	Ile	Val	Pro	Lys	Val	Asn	Tyr
370						375					380				
Thr	Ile	Tyr	Asp	Gly	Phe	Asn	Leu	Arg	Asn	Thr	Asn	Leu	Ala	Ala	Asn
385						390				395					400

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Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr Lys Leu  
 405 410 415  
 Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys Val Arg  
 420 425 430  
 Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Asp Lys Gly Tyr Asn Lys  
 435 440 445  
 Ile Glu Gly Arg Cys Asp Gly Ala Leu Asn Asp Leu Cys Ile Lys Val  
 450 455 460  
 Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn  
 465 470 475 480  
 Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala  
 485 490 495  
 Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr  
 500 505 510  
 Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser  
 515 520 525  
 Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe  
 530 535 540  
 Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr  
 545 550 555 560  
 Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr  
 565 570 575  
 Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe  
 580 585 590  
 Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala  
 595 600 605  
 Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu  
 610 615 620  
 Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile  
 625 630 635 640  
 Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys  
 645 650 655  
 Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu  
 660 665 670  
 Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu  
 675 680 685  
 Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn  
 690 695 700  
 Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile  
 705 710 715 720  
 Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg  
 725 730 735  
 Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala  
 740 745 750

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Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn
      755                      760                      765

Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile
      770                      775                      780

Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val
      785                      790                      795                      800

Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu
      805                      810                      815

Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp
      820                      825                      830

Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val
      835                      840                      845

Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val
      850                      855                      860

Asp Asn Gln Arg Leu Leu Ser Thr Phe Thr Glu Tyr Ile Lys Ser Gly
      865                      870                      875                      880

Leu Asn Ser Pro Gly Ala Ala His Tyr Ala Gln His Asp Glu Ala Val
      885                      890                      895

Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu
      900                      905                      910

His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn Ala Phe Ile Gln Ser
      915                      920                      925

Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Leu Leu Ala Glu Ala Lys
      930                      935                      940

Lys Leu Asn Asp Ala Gln Ala Pro Lys Val Asp Asn Lys Phe Asn Lys
      945                      950                      955                      960

Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu His Leu Pro Asn Leu Asn
      965                      970                      975

Glu Glu Gln Arg Asn Ala Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser
      980                      985                      990

Gln Ser Ala Asn Leu Leu Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln
      995                      1000                      1005

Ala Pro Lys Val Asp *
      1010

```

## (2) INFORMATION FOR SEQ ID NO: 19:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3509 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..3509

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:



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ATG CCA GTT ACA ATA AAT AAT TTT AAT TAT AAT GAT CCT ATT GAT AAT Met Pro Val Thr Ile Asn Asn Phe Asn Tyr Asn Asp Pro Ile Asp Asn 1 5 10 15	48
AAT AAT ATT ATT ATG ATG GAG CCT CCA TTT GCG AGA GGT ACG GGG AGA Asn Asn Ile Ile Met Met Glu Pro Pro Phe Ala Arg Gly Thr Gly Arg 20 25 30	96
TAT TAT AAA GCT TTT AAA ATC ACA GAT CGT ATT TGG ATA ATA CCG GAA Tyr Tyr Lys Ala Phe Lys Ile Thr Asp Arg Ile Trp Ile Ile Pro Glu 35 40 45	144
AGA TAT ACT TTT GGA TAT AAA CCT GAG GAT TTT AAT AAA AGT TCC GGT Arg Tyr Thr Phe Gly Tyr Lys Pro Glu Asp Phe Asn Lys Ser Ser Gly 50 55 60	192
ATT TTT AAT AGA GAT GTT TGT GAA TAT TAT GAT CCA GAT TAC TTA AAT Ile Phe Asn Arg Asp Val Cys Glu Tyr Tyr Asp Pro Asp Tyr Leu Asn 65 70 75 80	240
ACT AAT GAT AAA AAG AAT ATA TTT TTA CAA ACA ATG ATC AAG TTA TTT Thr Asn Asp Lys Lys Asn Ile Phe Leu Gln Thr Met Ile Lys Leu Phe 85 90 95	288
AAT AGA ATC AAA TCA AAA CCA TTG GGT GAA AAG TTA TTA GAG ATG ATT Asn Arg Ile Lys Ser Lys Pro Leu Gly Glu Lys Leu Leu Glu Met Ile 100 105 110	336
ATA AAT GGT ATA CCT TAT CTT GGA GAT AGA CGT GTT CCA CTC GAA GAG Ile Asn Gly Ile Pro Tyr Leu Gly Asp Arg Arg Val Pro Leu Glu Glu 115 120 125	384
TTT AAC ACA AAC ATT GCT AGT GTA ACT GTT AAT AAA TTA ATC AGT AAT Phe Asn Thr Asn Ile Ala Ser Val Thr Val Asn Lys Leu Ile Ser Asn 130 135 140	432
CCA GGA GAA GTG GAG CGA AAA AAA GGT ATT TTC GCA AAT TTA ATA ATA Pro Gly Glu Val Glu Arg Lys Lys Gly Ile Phe Ala Asn Leu Ile Ile 145 150 155 160	480
TTT GGA CCT GGG CCA GTT TTA AAT GAA AAT GAG ACT ATA GAT ATA GGT Phe Gly Pro Gly Pro Val Leu Asn Glu Asn Glu Thr Ile Asp Ile Gly 165 170 175	528
ATA CAA AAT CAT TTT GCA TCA AGG GAA GGC TTC GGG GGT ATA ATG CAA Ile Gln Asn His Phe Ala Ser Arg Glu Gly Phe Gly Gly Ile Met Gln 180 185 190	576
ATG AAG TTT TGC CCA GAA TAT GTA AGC GTA TTT AAT AAT GTT CAA GAA Met Lys Phe Cys Pro Glu Tyr Val Ser Val Phe Asn Asn Val Gln Glu 195 200 205	624
AAC AAA GGC GCA AGT ATA TTT AAT AGA CGT GGA TAT TTT TCA GAT CCA Asn Lys Gly Ala Ser Ile Phe Asn Arg Arg Gly Tyr Phe Ser Asp Pro 210 215 220	672
GCC TTG ATA TTA ATG CAT GAA CTT ATA CAT GTT TTA CAT GGA TTA TAT Ala Leu Ile Leu Met His Glu Leu Ile His Val Leu His Gly Leu Tyr 225 230 235 240	720
GGC ATT AAA GTA GAT GAT TTA CCA ATT GTA CCA AAT GAA AAA AAA TTT Gly Ile Lys Val Asp Asp Leu Pro Ile Val Pro Asn Glu Lys Lys Phe 245 250 255	768
TTT ATG CAA TCT ACA GAT GCT ATA CAG GCA GAA GAA CTA TAT ACA TTT Phe Met Gln Ser Thr Asp Ala Ile Gln Ala Glu Glu Leu Tyr Thr Phe 260 265 270	816

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GGA	GGA	CAA	GAT	CCC	AGC	ATC	ATA	ACT	CCT	TCT	ACG	GAT	AAA	AGT	ATC	864
Gly	Gly	Gln	Asp	Pro	Ser	Ile	Ile	Thr	Pro	Ser	Thr	Asp	Lys	Ser	Ile	
		275					280					285				
TAT	GAT	AAA	GTT	TTG	CAA	AAT	TTT	AGA	GGG	ATA	GTT	GAT	AGA	CTT	AAC	912
Tyr	Asp	Lys	Val	Leu	Gln	Asn	Phe	Arg	Gly	Ile	Val	Asp	Arg	Leu	Asn	
	290					295				300						
AAG	GTT	TTA	GTT	TGC	ATA	TCA	GAT	CCT	AAC	ATT	AAT	ATT	AAT	ATA	TAT	960
Lys	Val	Leu	Val	Cys	Ile	Ser	Asp	Pro	Asn	Ile	Asn	Ile	Asn	Ile	Tyr	
305					310					315					320	
AAA	AAT	AAA	TTT	AAA	GAT	AAA	TAT	AAA	TTC	GTT	GAA	GAT	TCT	GAG	GGA	1008
Lys	Asn	Lys	Phe	Lys	Asp	Lys	Tyr	Lys	Phe	Val	Glu	Asp	Ser	Glu	Gly	
				325					330					335		
AAA	TAT	AGT	ATA	GAT	GTA	GAA	AGT	TTT	GAT	AAA	TTA	TAT	AAA	AGC	TTA	1056
Lys	Tyr	Ser	Ile	Asp	Val	Glu	Ser	Phe	Asp	Lys	Leu	Tyr	Lys	Ser	Leu	
			340					345					350			
ATG	TTT	GGT	TTT	ACA	GAA	ACT	AAT	ATA	GCA	GAA	AAT	TAT	AAA	ATA	AAA	1104
Met	Phe	Gly	Phe	Thr	Glu	Thr	Asn	Ile	Ala	Glu	Asn	Tyr	Lys	Ile	Lys	
		355					360					365				
ACT	AGA	GCT	TCT	TAT	TTT	AGT	GAT	TCC	TTA	CCA	CCA	GTA	AAA	ATA	AAA	1152
Thr	Arg	Ala	Ser	Tyr	Phe	Ser	Asp	Ser	Leu	Pro	Pro	Val	Lys	Ile	Lys	
	370					375					380					
AAT	TTA	TTA	GAT	AAT	GAA	ATC	TAT	ACT	ATA	GAG	GAA	GGG	TTT	AAT	ATA	1200
Asn	Leu	Leu	Asp	Asn	Glu	Ile	Tyr	Thr	Ile	Glu	Glu	Gly	Phe	Asn	Ile	
385					390					395					400	
TCT	GAT	AAA	GAT	ATG	GAA	AAA	GAA	TAT	AGA	GGT	CAG	AAT	AAA	GCT	ATA	1248
Ser	Asp	Lys	Asp	Met	Glu	Lys	Glu	Tyr	Arg	Gly	Gln	Asn	Lys	Ala	Ile	
				405					410					415		
AAT	AAA	CAA	GCT	TAT	GAA	GAA	ATT	AGC	AAG	GAG	CAT	TTG	GCT	GTA	TAT	1296
Asn	Lys	Gln	Ala	Tyr	Glu	Glu	Ile	Ser	Lys	Glu	His	Leu	Ala	Val	Tyr	
			420					425					430			
AAG	ATA	CAA	ATG	TGT	AAA	AGT	GTT	AAA	GCT	CCA	GGA	ATA	TGT	ATT	GAT	1344
Lys	Ile	Gln	Met	Cys	Lys	Ser	Val	Lys	Ala	Pro	Gly	Ile	Cys	Ile	Asp	
		435					440					445				
GTT	GAT	AAT	GAA	GAT	TTG	TTC	TTT	ATA	GCT	GAT	AAA	AAT	AGT	TTT	TCA	1392
Val	Asp	Asn	Glu	Asp	Leu	Phe	Phe	Ile	Ala	Asp	Lys	Asn	Ser	Phe	Ser	
	450					455					460					
GAT	GAT	TTA	TCT	AAA	AAC	GAA	AGA	ATA	GAA	TAT	AAT	ACA	CAG	AGT	AAT	1440
Asp	Asp	Leu	Ser	Lys	Asn	Glu	Arg	Ile	Glu	Tyr	Asn	Thr	Gln	Ser	Asn	
465					470					475					480	
TAT	ATA	GAA	AAT	GAC	TTC	CCT	ATA	AAT	GAA	TTA	ATT	TTA	GAT	ACT	GAT	1488
Tyr	Ile	Glu	Asn	Asp	Phe	Pro	Ile	Asn	Glu	Leu	Ile	Leu	Asp	Thr	Asp	
				485					490					495		
TTA	ATA	AGT	AAA	ATA	GAA	TTA	CCA	AGT	GAA	AAT	ACA	GAA	TCA	CTT	ACT	1536
Leu	Ile	Ser	Lys	Ile	Glu	Leu	Pro	Ser	Glu	Asn	Thr	Glu	Ser	Leu	Thr	
			500					505					510			
GAT	TTT	AAT	GTA	GAT	GTT	CCA	GTA	TAT	GAA	AAA	CAA	CCC	GCT	ATA	AAA	1584
Asp	Phe	Asn	Val	Asp	Val	Pro	Val	Tyr	Glu	Lys	Gln	Pro	Ala	Ile	Lys	
		515					520					525				
AAA	ATT	TTT	ACA	GAT	GAA	AAT	ACC	ATC	TTT	CAA	TAT	TTA	TAC	TCT	CAG	1632
Lys	Ile	Phe	Thr	Asp	Glu	Asn	Thr	Ile	Phe	Gln	Tyr	Leu	Tyr	Ser	Gln	
	530					535					540					

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ACA TTT CCT CTA GAT ATA AGA GAT ATA AGT TTA ACA TCT TCA TTT GAT Thr Phe Pro Leu Asp Ile Arg Asp Ile Ser Leu Thr Ser Ser Phe Asp 545 550 555 560	1680
GAT GCA TTA TTA TTT TCT AAC AAA GTT TAT TCA TTT TTT TCT ATG GAT Asp Ala Leu Leu Phe Ser Asn Lys Val Tyr Ser Phe Phe Ser Met Asp 565 570 575	1728
TAT ATT AAA ACT GCT AAT AAA GTG GTA GAA GCA GGA TTA TTT GCA GGT Tyr Ile Lys Thr Ala Asn Lys Val Val Glu Ala Gly Leu Phe Ala Gly 580 585 590	1776
TGG GTG AAA CAG ATA GTA AAT GAT TTT GTA ATC GAA GCT AAT AAA AGC Trp Val Lys Gln Ile Val Asn Asp Phe Val Ile Glu Ala Asn Lys Ser 595 600 605	1824
AAT ACT ATG GAT AAA ATT GCA GAT ATA TCT CTA ATT GTT CCT TAT ATA Asn Thr Met Asp Lys Ile Ala Asp Ile Ser Leu Ile Val Pro Tyr Ile 610 615 620	1872
GGA TTA GCT TTA AAT GTA GGA AAT GAA ACA GCT AAA GGA AAT TTT GAA Gly Leu Ala Leu Asn Val Gly Asn Glu Thr Ala Lys Gly Asn Phe Glu 625 630 635 640	1920
AAT GCT TTT GAG ATT GCA GGA GCC AGT ATT CTA CTA GAA TTT ATA CCA Asn Ala Phe Glu Ile Ala Gly Ala Ser Ile Leu Leu Glu Phe Ile Pro 645 650 655	1968
GAA CTT TTA ATA CCT GTA GTT GGA GCC TTT TTA TTA GAA TCA TAT ATT Glu Leu Leu Ile Pro Val Val Gly Ala Phe Leu Leu Glu Ser Tyr Ile 660 665 670	2016
GAC AAT AAA AAT AAA ATT ATT AAA ACA ATA GAT AAT GCT TTA ACT AAA Asp Asn Lys Asn Lys Ile Ile Lys Thr Ile Asp Asn Ala Leu Thr Lys 675 680 685	2064
AGA AAT GAA AAA TGG AGT GAT ATG TAC GGA TTA ATA GTA GCG CAA TGG Arg Asn Glu Lys Trp Ser Asp Met Tyr Gly Leu Ile Val Ala Gln Trp 690 695 700	2112
CTC TCA ACA GTT AAT ACT CAA TTT TAT ACA ATA AAA GAG GGA ATG TAT Leu Ser Thr Val Asn Thr Gln Phe Tyr Thr Ile Lys Glu Gly Met Tyr 705 710 715 720	2160
AAG GCT TTA AAT TAT CAA GCA CAA GCA TTG GAA GAA ATA ATA AAA TAC Lys Ala Leu Asn Tyr Gln Ala Gln Ala Leu Glu Glu Ile Ile Lys Tyr 725 730 735	2208
AGA TAT AAT ATA TAT TCT GAA AAA GAA AAG TCA AAT ATT AAC ATC GAT Arg Tyr Asn Ile Tyr Ser Glu Lys Glu Lys Ser Asn Ile Asn Ile Asp 740 745 750	2256
TTT AAT GAT ATA AAT TCT AAA CTT AAT GAG GGT ATT AAC CAA GCT ATA Phe Asn Asp Ile Asn Ser Lys Leu Asn Glu Gly Ile Asn Gln Ala Ile 755 760 765	2304
GAT AAT ATA AAT AAT TTT ATA AAT GGA TGT TCT GTA TCA TAT TTA ATG Asp Asn Ile Asn Asn Phe Ile Asn Gly Cys Ser Val Ser Tyr Leu Met 770 775 780	2352
AAA AAA ATG ATT CCA TTA GCT GTA GAA AAA TTA CTA GAC TTT GAT AAT Lys Lys Met Ile Pro Leu Ala Val Glu Lys Leu Leu Asp Phe Asp Asn 785 790 795 800	2400
ACT CTC AAA AAA AAT TTG TTA AAT TAT ATA GAT GAA AAT AAA TTA TAT Thr Leu Lys Lys Asn Leu Leu Asn Tyr Ile Asp Glu Asn Lys Leu Tyr 805 810 815	2448

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TTG ATT GGA AGT GCA GAA TAT GAA AAA TCA AAA GTA AAT AAA TAC TTG Leu Ile Gly Ser 820 Ala Glu Tyr Glu Lys 825 Ser Lys Val Asn Lys 830 Tyr Leu	2496
AAA ACC ATT ATG CCG TTT GAT CTT TCA ATA TAT ACC AAT GAT ACA ATA Lys Thr 835 Ile Met Pro Phe Asp Leu Ser 840 Ile Tyr Thr Asn Asp 845 Thr Ile	2544
CTA ATA GAA ATG TTT AAT AAA TAT AAT AGC GAA ATT TTA AAT AAT ATT Leu Ile 850 Glu Met Phe Asn Lys 855 Tyr Asn Ser Glu Ile 860 Leu Asn Asn Ile	2592
ATC TTA AAT TTA AGA TAT AAG GAT AAT AAT TTA ATA GAT TTA TCA GGA Ile Leu Asn Leu Arg Tyr Lys Asp Asn Asn 870 Leu Ile Asp Leu Ser Gly 880 865	2640
TAT GGG GCA AAG GTA GAG GTA TAT GAT GGA GTC GAG CTT AAT GAT AAA Tyr Gly Ala Lys 885 Val Glu Val Tyr Asp Gly 890 Val Glu Leu Asn Asp 895 Lys	2688
AAT CAA TTT AAA TTA ACT AGT TCA GCA AAT AGT AAG ATT AGA GTG ACT Asn Gln Phe Lys 900 Leu Thr Ser Ser 905 Ala Asn Ser Lys Ile 910 Arg Val Thr	2736
CAA AAT CAG AAT ATC ATA TTT AAT AGT GTG TTC CTT GAT TTT AGC GTT Gln Asn Gln Asn Ile Ile Phe 920 Asn Ser Val Phe Leu Asp 925 Phe Ser Val	2784
AGC TTT TGG ATA AGA ATA CCT AAA TAT AAG AAT GAT GGT ATA CAA AAT Ser Phe Trp Ile Arg Ile 935 Pro Lys Tyr Lys Asn Asp 940 Gly Ile Gln Asn	2832
TAT ATT CAT AAT GAA TAT ACA ATA ATT AAT TGT ATG AAA AAT AAT TCG Tyr Ile His Asn Glu Tyr Thr Ile Ile Asn 950 Cys Met Lys Asn Asn Ser 960 945	2880
GGC TGG AAA ATA TCT ATT AGG GGT AAT AGG ATA ATA TGG ACT TTA ATT Gly Trp Lys Ile Ser Ile Arg Gly Asn 970 Arg Ile Ile Trp Thr Leu Ile 975	2928
GAT ATA AAT GGA AAA ACC AAA TCG GTA TTT TTT GAA TAT AAC ATA AGA Asp Ile Asn Gly 980 Lys Thr Lys Ser Val Phe Phe Glu Tyr Asn Ile Arg 990 985	2976
GAA GAT ATA TCA GAG TAT ATA AAT AGA TGG TTT TTT GTA ACT ATT ACT Glu Asp Ile Ser Glu Tyr Ile Asn Arg Trp Phe Phe Val Thr Ile Thr 1005 995 1000	3024
AAT AAT TTG AAT AAC GCT AAA ATT TAT ATT AAT GGT AAG CTA GAA TCA Asn Asn Leu Asn Asn Ala Lys Ile Tyr Ile Asn Gly Lys Leu Glu Ser 1020 1010 1015	3072
AAT ACA GAT ATT AAA GAT ATA AGA GAA GTT ATT GCT AAT GGT GAA ATA Asn Thr Asp Ile Lys Asp Ile Arg Glu Val Ile Ala Asn Gly Glu Ile 1040 1025 1030 1035	3120
ATA TTT AAA TTA GAT GGT GAT ATA GAT AGA ACA CAA TTT ATT TGG ATG Ile Phe Lys Leu Asp Gly Asp Ile Asp Arg Thr Gln Phe Ile Trp Met 1055 1045 1050	3168
AAA TAT TTC AGT ATT TTT AAT ACG GAA TTA AGT CAA TCA AAT ATT GAA Lys Tyr Phe Ser Ile Phe Asn Thr Glu Leu Ser Gln Ser Asn Ile Glu 1070 1060 1065	3216
GAA AGA TAT AAA ATT CAA TCA TAT AGC GAA TAT TTA AAA GAT TTT TGG Glu Arg Tyr Lys Ile Gln Ser Tyr Ser Glu Tyr Leu Lys Asp Phe Trp 1085 1075 1080	3264

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GGA AAT CCT TTA ATG TAC AAT AAA GAA TAT TAT ATG TTT AAT GCG GGG Gly Asn Pro Leu Met Tyr Asn Lys Glu Tyr Tyr Met Phe Asn Ala Gly 1090 1095 1100	3312
AAT AAA AAT TCA TAT ATT AAA CTA AAG AAA GAT TCA CCT GTA GGT GAA Asn Lys Asn Ser Tyr Ile Lys Leu Lys Lys Asp Ser Pro Val Gly Glu 1105 1110 1115 1120	3360
ATT TTA ACA CGT AGC AAA TAT AAT CAA AAT TCT AAA TAT ATA AAT TAT Ile Leu Thr Arg Ser Lys Tyr Asn Gln Asn Ser Lys Tyr Ile Asn Tyr 1125 1130 1135	3408
AGA GAT TTA TAT ATT GGA GAA AAA TTT ATT ATA AGA AGA AAG TCA AAT Arg Asp Leu Tyr Ile Gly Glu Lys Phe Ile Ile Arg Arg Lys Ser Asn 1140 1145 1150	3456
TCT CAA TCT ATA AAT GAT GAT ATA GTT AGA AAA GAA GAT TAT ATA TAT Ser Gln Ser Ile Asn Asp Asp Ile Val Arg Lys Glu Asp Tyr Ile Tyr 1155 1160 1165	3504
CTA GA Leu	3509

## (2) INFORMATION FOR SEQ ID NO: 20:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1169 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

Met Pro Val Thr Ile Asn Asn Phe Asn Tyr Asn Asp Pro Ile Asp Asn 1 5 10 15
Asn Asn Ile Ile Met Met Glu Pro Pro Phe Ala Arg Gly Thr Gly Arg 20 25 30
Tyr Tyr Lys Ala Phe Lys Ile Thr Asp Arg Ile Trp Ile Ile Pro Glu 35 40 45
Arg Tyr Thr Phe Gly Tyr Lys Pro Glu Asp Phe Asn Lys Ser Ser Gly 50 55 60
Ile Phe Asn Arg Asp Val Cys Glu Tyr Tyr Asp Pro Asp Tyr Leu Asn 65 70 75 80
Thr Asn Asp Lys Lys Asn Ile Phe Leu Gln Thr Met Ile Lys Leu Phe 85 90 95
Asn Arg Ile Lys Ser Lys Pro Leu Gly Glu Lys Leu Leu Glu Met Ile 100 105 110
Ile Asn Gly Ile Pro Tyr Leu Gly Asp Arg Arg Val Pro Leu Glu Glu 115 120 125
Phe Asn Thr Asn Ile Ala Ser Val Thr Val Asn Lys Leu Ile Ser Asn 130 135 140
Pro Gly Glu Val Glu Arg Lys Lys Gly Ile Phe Ala Asn Leu Ile Ile 145 150 155 160
Phe Gly Pro Gly Pro Val Leu Asn Glu Asn Glu Thr Ile Asp Ile Gly 165 170 175

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Ile Gln Asn His Phe Ala Ser Arg Glu Gly Phe Gly Gly Ile Met Gln  
 180 185 190  
 Met Lys Phe Cys Pro Glu Tyr Val Ser Val Phe Asn Asn Val Gln Glu  
 195 200 205  
 Asn Lys Gly Ala Ser Ile Phe Asn Arg Arg Gly Tyr Phe Ser Asp Pro  
 210 215 220  
 Ala Leu Ile Leu Met His Glu Leu Ile His Val Leu His Gly Leu Tyr  
 225 230 235 240  
 Gly Ile Lys Val Asp Asp Leu Pro Ile Val Pro Asn Glu Lys Lys Phe  
 245 250 255  
 Phe Met Gln Ser Thr Asp Ala Ile Gln Ala Glu Glu Leu Tyr Thr Phe  
 260 265 270  
 Gly Gly Gln Asp Pro Ser Ile Ile Thr Pro Ser Thr Asp Lys Ser Ile  
 275 280 285  
 Tyr Asp Lys Val Leu Gln Asn Phe Arg Gly Ile Val Asp Arg Leu Asn  
 290 295 300  
 Lys Val Leu Val Cys Ile Ser Asp Pro Asn Ile Asn Ile Asn Ile Tyr  
 305 310 315 320  
 Lys Asn Lys Phe Lys Asp Lys Tyr Lys Phe Val Glu Asp Ser Glu Gly  
 325 330 335  
 Lys Tyr Ser Ile Asp Val Glu Ser Phe Asp Lys Leu Tyr Lys Ser Leu  
 340 345 350  
 Met Phe Gly Phe Thr Glu Thr Asn Ile Ala Glu Asn Tyr Lys Ile Lys  
 355 360 365  
 Thr Arg Ala Ser Tyr Phe Ser Asp Ser Leu Pro Pro Val Lys Ile Lys  
 370 375 380  
 Asn Leu Leu Asp Asn Glu Ile Tyr Thr Ile Glu Glu Gly Phe Asn Ile  
 385 390 395 400  
 Ser Asp Lys Asp Met Glu Lys Glu Tyr Arg Gly Gln Asn Lys Ala Ile  
 405 410 415  
 Asn Lys Gln Ala Tyr Glu Glu Ile Ser Lys Glu His Leu Ala Val Tyr  
 420 425 430  
 Lys Ile Gln Met Cys Lys Ser Val Lys Ala Pro Gly Ile Cys Ile Asp  
 435 440 445  
 Val Asp Asn Glu Asp Leu Phe Phe Ile Ala Asp Lys Asn Ser Phe Ser  
 450 455 460  
 Asp Asp Leu Ser Lys Asn Glu Arg Ile Glu Tyr Asn Thr Gln Ser Asn  
 465 470 475 480  
 Tyr Ile Glu Asn Asp Phe Pro Ile Asn Glu Leu Ile Leu Asp Thr Asp  
 485 490 495  
 Leu Ile Ser Lys Ile Glu Leu Pro Ser Glu Asn Thr Glu Ser Leu Thr  
 500 505 510  
 Asp Phe Asn Val Asp Val Pro Val Tyr Glu Lys Gln Pro Ala Ile Lys  
 515 520 525

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Lys Ile Phe Thr Asp Glu Asn Thr Ile Phe Gln Tyr Leu Tyr Ser Gln  
 530 535 540  
 Thr Phe Pro Leu Asp Ile Arg Asp Ile Ser Leu Thr Ser Ser Phe Asp  
 545 550 555 560  
 Asp Ala Leu Leu Phe Ser Asn Lys Val Tyr Ser Phe Phe Ser Met Asp  
 565 570 575  
 Tyr Ile Lys Thr Ala Asn Lys Val Val Glu Ala Gly Leu Phe Ala Gly  
 580 585 590  
 Trp Val Lys Gln Ile Val Asn Asp Phe Val Ile Glu Ala Asn Lys Ser  
 595 600 605  
 Asn Thr Met Asp Lys Ile Ala Asp Ile Ser Leu Ile Val Pro Tyr Ile  
 610 615 620  
 Gly Leu Ala Leu Asn Val Gly Asn Glu Thr Ala Lys Gly Asn Phe Glu  
 625 630 635 640  
 Asn Ala Phe Glu Ile Ala Gly Ala Ser Ile Leu Leu Glu Phe Ile Pro  
 645 650 655  
 Glu Leu Leu Ile Pro Val Val Gly Ala Phe Leu Leu Glu Ser Tyr Ile  
 660 665 670  
 Asp Asn Lys Asn Lys Ile Ile Lys Thr Ile Asp Asn Ala Leu Thr Lys  
 675 680 685  
 Arg Asn Glu Lys Trp Ser Asp Met Tyr Gly Leu Ile Val Ala Gln Trp  
 690 695 700  
 Leu Ser Thr Val Asn Thr Gln Phe Tyr Thr Ile Lys Glu Gly Met Tyr  
 705 710 715 720  
 Lys Ala Leu Asn Tyr Gln Ala Gln Ala Leu Glu Glu Ile Ile Lys Tyr  
 725 730 735  
 Arg Tyr Asn Ile Tyr Ser Glu Lys Glu Lys Ser Asn Ile Asn Ile Asp  
 740 745 750  
 Phe Asn Asp Ile Asn Ser Lys Leu Asn Glu Gly Ile Asn Gln Ala Ile  
 755 760 765  
 Asp Asn Ile Asn Asn Phe Ile Asn Gly Cys Ser Val Ser Tyr Leu Met  
 770 775 780  
 Lys Lys Met Ile Pro Leu Ala Val Glu Lys Leu Leu Asp Phe Asp Asn  
 785 790 795 800  
 Thr Leu Lys Lys Asn Leu Leu Asn Tyr Ile Asp Glu Asn Lys Leu Tyr  
 805 810 815  
 Leu Ile Gly Ser Ala Glu Tyr Glu Lys Ser Lys Val Asn Lys Tyr Leu  
 820 825 830  
 Lys Thr Ile Met Pro Phe Asp Leu Ser Ile Tyr Thr Asn Asp Thr Ile  
 835 840 845  
 Leu Ile Glu Met Phe Asn Lys Tyr Asn Ser Glu Ile Leu Asn Asn Ile  
 850 855 860  
 Ile Leu Asn Leu Arg Tyr Lys Asp Asn Asn Leu Ile Asp Leu Ser Gly  
 865 870 875 880

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[illegible]

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:

- SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 2574 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)



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## (ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION:1..2574

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

ATG CCA GTT ACA ATA AAT AAT TTT AAT TAT AAT GAT CCT ATT GAT AAT	48
Met Pro Val Thr Ile Asn Asn Phe Asn Tyr Asn Asp Pro Ile Asp Asn	
1 5 10 15	
AAT AAT ATT ATT ATG ATG GAG CCT CCA TTT GCG AGA GGT ACG GGG AGA	96
Asn Asn Ile Ile Met Met Glu Pro Pro Phe Ala Arg Gly Thr Gly Arg	
20 25 30	
TAT TAT AAA GCT TTT AAA ATC ACA GAT CGT ATT TGG ATA ATA CCG GAA	144
Tyr Tyr Lys Ala Phe Lys Ile Thr Asp Arg Ile Trp Ile Ile Pro Glu	
35 40 45	
AGA TAT ACT TTT GGA TAT AAA CCT GAG GAT TTT AAT AAA AGT TCC GGT	192
Arg Tyr Thr Phe Gly Tyr Lys Pro Glu Asp Phe Asn Lys Ser Ser Gly	
50 55 60	
ATT TTT AAT AGA GAT GTT TGT GAA TAT TAT GAT CCA GAT TAC TTA AAT	240
Ile Phe Asn Arg Asp Val Cys Glu Tyr Tyr Asp Pro Asp Tyr Leu Asn	
65 70 75 80	
ACT AAT GAT AAA AAG AAT ATA TTT TTA CAA ACA ATG ATC AAG TTA TTT	288
Thr Asn Asp Lys Lys Asn Ile Phe Leu Gln Thr Met Ile Lys Leu Phe	
85 90 95	
AAT AGA ATC AAA TCA AAA CCA TTG GGT GAA AAG TTA TTA GAG ATG ATT	336
Asn Arg Ile Lys Ser Lys Pro Leu Gly Glu Lys Leu Leu Glu Met Ile	
100 105 110	
ATA AAT GGT ATA CCT TAT CTT GGA GAT AGA CGT GTT CCA CTC GAA GAG	384
Ile Asn Gly Ile Pro Tyr Leu Gly Asp Arg Arg Val Pro Leu Glu Glu	
115 120 125	
TTT AAC ACA AAC ATT GCT AGT GTA ACT GTT AAT AAA TTA ATC AGT AAT	432
Phe Asn Thr Asn Ile Ala Ser Val Thr Val Asn Lys Leu Ile Ser Asn	
130 135 140	
CCA GGA GAA GTG GAG CGA AAA AAA GGT ATT TTC GCA AAT TTA ATA ATA	480
Pro Gly Glu Val Glu Arg Lys Lys Gly Ile Phe Ala Asn Leu Ile Ile	
145 150 155 160	
TTT GGA CCT GGG CCA GTT TTA AAT GAA AAT GAG ACT ATA GAT ATA GGT	528
Phe Gly Pro Gly Pro Val Leu Asn Glu Asn Glu Thr Ile Asp Ile Gly	
165 170 175	
ATA CAA AAT CAT TTT GCA TCA AGG GAA GGC TTC GGG GGT ATA ATG CAA	576
Ile Gln Asn His Phe Ala Ser Arg Glu Gly Phe Gly Gly Ile Met Gln	
180 185 190	
ATG AAG TTT TGC CCA GAA TAT GTA AGC GTA TTT AAT AAT GTT CAA GAA	624
Met Lys Phe Cys Pro Glu Tyr Val Ser Val Phe Asn Asn Val Gln Glu	
195 200 205	
AAC AAA GGC GCA AGT ATA TTT AAT AGA CGT GGA TAT TTT TCA GAT CCA	672
Asn Lys Gly Ala Ser Ile Phe Asn Arg Arg Gly Tyr Phe Ser Asp Pro	
210 215 220	
GCC TTG ATA TTA ATG CAT GAA CTT ATA CAT GTT TTA CAT GGA TTA TAT	720
Ala Leu Ile Leu Met His Glu Leu Ile His Val Leu His Gly Leu Tyr	
225 230 235 240	

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GGC	ATT	AAA	GTA	GAT	GAT	TTA	CCA	ATT	GTA	CCA	AAT	GAA	AAA	AAA	TTT	768
Gly	Ile	Lys	Val	Asp	Asp	Leu	Pro	Ile	Val	Pro	Asn	Glu	Lys	Lys	Phe	
				245					250					255		
TTT	ATG	CAA	TCT	ACA	GAT	GCT	ATA	CAG	GCA	GAA	GAA	CTA	TAT	ACA	TTT	816
Phe	Met	Gln	Ser	Thr	Asp	Ala	Ile	Gln	Ala	Glu	Glu	Leu	Tyr	Thr	Phe	
			260					265					270			
GGA	GGA	CAA	GAT	CCC	AGC	ATC	ATA	ACT	CCT	TCT	ACG	GAT	AAA	AGT	ATC	864
Gly	Gly	Gln	Asp	Pro	Ser	Ile	Ile	Thr	Pro	Ser	Thr	Asp	Lys	Ser	Ile	
		275					280					285				
TAT	GAT	AAA	GTT	TTG	CAA	AAT	TTT	AGA	GGG	ATA	GTT	GAT	AGA	CTT	AAC	912
Tyr	Asp	Lys	Val	Leu	Gln	Asn	Phe	Arg	Gly	Ile	Val	Asp	Arg	Leu	Asn	
	290					295					300					
AAG	GTT	TTA	GTT	TGC	ATA	TCA	GAT	CCT	AAC	ATT	AAT	ATT	AAT	ATA	TAT	960
Lys	Val	Leu	Val	Cys	Ile	Ser	Asp	Pro	Asn	Ile	Asn	Ile	Asn	Ile	Tyr	
305				310						315					320	
AAA	AAT	AAA	TTT	AAA	GAT	AAA	TAT	AAA	TTC	GTT	GAA	GAT	TCT	GAG	GGA	1008
Lys	Asn	Lys	Phe	Lys	Asp	Lys	Tyr	Lys	Phe	Val	Glu	Asp	Ser	Glu	Gly	
				325					330					335		
AAA	TAT	AGT	ATA	GAT	GTA	GAA	AGT	TTT	GAT	AAA	TTA	TAT	AAA	AGC	TTA	1056
Lys	Tyr	Ser	Ile	Asp	Val	Glu	Ser	Phe	Asp	Lys	Leu	Tyr	Lys	Ser	Leu	
			340					345					350			
ATG	TTT	GGT	TTT	ACA	GAA	ACT	AAT	ATA	GCA	GAA	AAT	TAT	AAA	ATA	AAA	1104
Met	Phe	Gly	Phe	Thr	Glu	Thr	Asn	Ile	Ala	Glu	Asn	Tyr	Lys	Ile	Lys	
		355					360					365				
ACT	AGA	GCT	TCT	TAT	TTT	AGT	GAT	TCC	TTA	CCA	CCA	GTA	AAA	ATA	AAA	1152
Thr	Arg	Ala	Ser	Tyr	Phe	Ser	Asp	Ser	Leu	Pro	Pro	Val	Lys	Ile	Lys	
	370					375					380					
AAT	TTA	TTA	GAT	AAT	GAA	ATC	TAT	ACT	ATA	GAG	GAA	GGG	TTT	AAT	ATA	1200
Asn	Leu	Leu	Asp	Asn	Glu	Ile	Tyr	Thr	Ile	Glu	Glu	Gly	Phe	Asn	Ile	
385					390					395					400	
TCT	GAT	AAA	GAT	ATG	GAA	AAA	GAA	TAT	AGA	GGT	CAG	AAT	AAA	GCT	ATA	1248
Ser	Asp	Lys	Asp	Met	Glu	Lys	Glu	Tyr	Arg	Gly	Gln	Asn	Lys	Ala	Ile	
				405					410					415		
AAT	AAA	CAA	GCT	TAT	GAA	GAA	ATT	AGC	AAG	GAG	CAT	TTG	GCT	GTA	TAT	1296
Asn	Lys	Gln	Ala	Tyr	Glu	Glu	Ile	Ser	Lys	Glu	His	Leu	Ala	Val	Tyr	
			420					425					430			
AAG	ATA	CAA	ATG	TGT	AAA	AGT	GTT	AAA	GCT	CCA	GGA	ATA	TGT	ATT	GAT	1344
Lys	Ile	Gln	Met	Cys	Lys	Ser	Val	Lys	Ala	Pro	Gly	Ile	Cys	Ile	Asp	
		435					440					445				
GTT	GAT	AAT	GAA	GAT	TTG	TTC	TTT	ATA	GCT	GAT	AAA	AAT	AGT	TTT	TCA	1392
Val	Asp	Asn	Glu	Asp	Leu	Phe	Phe	Ile	Ala	Asp	Lys	Asn	Ser	Phe	Ser	
	450					455					460					
GAT	GAT	TTA	TCT	AAA	AAC	GAA	AGA	ATA	GAA	TAT	AAT	ACA	CAG	AGT	AAT	1440
Asp	Asp	Leu	Ser	Lys	Asn	Glu	Arg	Ile	Glu	Tyr	Asn	Thr	Gln	Ser	Asn	
465					470					475					480	
TAT	ATA	GAA	AAT	GAC	TTC	CCT	ATA	AAT	GAA	TTA	ATT	TTA	GAT	ACT	GAT	1488
Tyr	Ile	Glu	Asn	Asp	Phe	Pro	Ile	Asn	Glu	Leu	Ile	Leu	Asp	Thr	Asp	
				485					490					495		
<del>TTA</del>	<del>ATA</del>	<del>AGT</del>	<del>AAA</del>	<del>ATA</del>	<del>GAA</del>	<del>TTA</del>	<del>CCA</del>	<del>AGT</del>	<del>GAA</del>	<del>AAT</del>	<del>ACA</del>	<del>GAA</del>	<del>TCA</del>	<del>GTT</del>	<del>ACT</del>	<del>1536</del>
<del>Leu</del>	<del>Ile</del>	<del>Ser</del>	<del>Lys</del>	<del>Ile</del>	<del>Glu</del>	<del>Leu</del>	<del>Pro</del>	<del>Ser</del>	<del>Glu</del>	<del>Asn</del>	<del>Thr</del>	<del>Glu</del>	<del>Ser</del>	<del>Leu</del>	<del>Thr</del>	
			500					505					510			

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GAT Asp	TTT Phe	AAT Asn 515	GTA Val	GAT Asp	GTT Val	CCA Pro	GTA Val 520	TAT Tyr	GAA Glu	AAA Lys	CAA Gln	CCC Pro 525	GCT Ala	ATA Ile	AAA Lys	1584
AAA Lys	ATT Ile 530	TTT Phe	ACA Thr	GAT Asp	GAA Glu	AAT Asn 535	ACC Thr	ATC Ile	TTT Phe	CAA Gln 540	TAT Tyr	TTA Leu	TAC Tyr	TCT Ser	CAG Gln	1632
ACA Thr 545	TTT Phe	CCT Pro	CTA Leu	GAT Asp	ATA Ile 550	AGA Arg	GAT Asp	ATA Ile	AGT Ser	TTA Leu 555	ACA Thr	TCT Ser	TCA Ser	TTT Phe	GAT Asp 560	1680
GAT Asp	GCA Ala	TTA Leu	TTA Leu	TTT Phe 565	TCT Ser	AAC Asn	AAA Lys	GTT Val	TAT Tyr 570	TCA Ser	TTT Phe	TTT Phe	TCT Ser	ATG Met 575	GAT Asp	1728
TAT Tyr	ATT Ile	AAA Lys	ACT Thr 580	GCT Ala	AAT Asn	AAA Lys	GTG Val	GTA Val	GAA Glu	GCA Ala	GGA Gly	TTA Leu	TTT Phe 590	GCA Ala	GGT Gly	1776
TGG Trp	GTG Val	AAA Lys 595	CAG Gln	ATA Ile	GTA Val	AAT Asn	GAT Asp 600	TTT Phe	GTA Val	ATC Ile	GAA Glu	GCT Ala 605	AAT Asn	AAA Lys	AGC Ser	1824
AAT Asn 610	ACT Thr	ATG Met	GAT Asp	AAA Lys	ATT Ile	GCA Ala 615	GAT Asp	ATA Ile	TCT Ser	CTA Leu	ATT Ile 620	GTT Val	CCT Pro	TAT Tyr	ATA Ile	1872
GGA Gly 625	TTA Leu	GCT Ala	TTA Leu	AAT Asn	GTA Val 630	GGA Gly	AAT Asn	GAA Glu	ACA Thr	GCT Ala 635	AAA Lys	GGA Gly	AAT Asn	TTT Phe	GAA Glu 640	1920
AAT Asn	GCT Ala	TTT Phe	GAG Glu 645	ATT Ile	GCA Ala	GGA Gly	GCC Ala	AGT Ser	ATT Ile 650	CTA Leu	CTA Leu	GAA Glu	TTT Phe	ATA Ile 655	CCA Pro	1968
GAA Glu	CTT Leu	TTA Leu	ATA Ile 660	CCT Pro	GTA Val	GTT Val	GGA Gly	GCC Ala	TTT Phe 665	TTA Leu	TTA Leu	GAA Glu	TCA Ser 670	TAT Tyr	ATT Ile	2016
GAC Asp	AAT Asn	AAA Lys 675	AAT Asn	AAA Lys	ATT Ile	ATT Ile	AAA Lys 680	ACA Thr	ATA Ile	GAT Asp	AAT Asn	GCT Ala 685	TTA Leu	ACT Thr	AAA Lys	2064
AGA Arg 690	AAT Asn	GAA Glu	AAA Lys	TGG Trp	AGT Ser	GAT Asp 695	ATG Met	TAC Tyr	GGA Gly	TTA Leu 700	ATA Ile	GTA Val	GCG Ala	CAA Gln	TGG Trp	2112
CTC Leu 705	TCA Ser	ACA Thr	GTT Val	AAT Asn	ACT Thr 710	CAA Gln	TTT Phe	TAT Tyr	ACA Thr 715	ATA Ile	AAA Lys	GAG Glu	GGA Gly	ATG Met 720	TAT Tyr	2160
AAG Lys	GCT Ala	TTA Leu	AAT Asn	TAT Tyr 725	CAA Gln	GCA Ala	CAA Gln	GCA Ala	TTG Leu 730	GAA Glu	GAA Glu	ATA Ile	ATA Ile	AAA Lys 735	TAC Tyr	2208
AGA Arg	TAT Tyr	AAT Asn	ATA Ile 740	TAT Tyr	TCT Ser	GAA Glu	AAA Lys	GAA Glu	AAG Lys	TCA Ser	AAT Asn	ATT Ile 750	AAC Asn	ATC Ile	GAT Asp	2256
TTT Phe	AAT Asn	GAT Asp 755	ATA Ile	AAT Asn	TCT Ser	AAA Lys	CTT Leu 760	AAT Asn	GAG Glu	GGT Gly	ATT Ile 765	AAC Asn	CAA Gln	GCT Ala	ATA Ile	2304
GAT Asp 770	AAT Asn	ATA Ile	AAT Asn	AAT Asn	TTT Phe 775	ATA Ile	AAT Asn	GGA Gly	TGT Cys	TCT Ser	GTA Val 780	TCA Ser	TAT Tyr	TTA Leu	ATG Met	2352

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AAA AAA ATG ATT CCA TTA GCT GTA GAA AAA TTA CTA GAC TTT GAT AAT Lys Lys Met Ile Pro Leu Ala Val Glu Lys Leu Leu Asp Phe Asp Asn 785 790 795 800	2400
ACT CTC AAA AAA AAT TTG TTA AAT TAT ATA GAT GAA AAT AAA TTA TAT Thr Leu Lys Lys Asn Leu Leu Asn Tyr Ile Asp Glu Asn Lys Leu Tyr 805 810 815	2448
TTG ATT GGA AGT GCA GAA TAT GAA AAA TCA AAA GTA AAT AAA TAC TTG Leu Ile Gly Ser Ala Glu Tyr Glu Lys Ser Lys Val Asn Lys Tyr Leu 820 825 830	2496
AAA ACC ATT ATG CCG TTT GAT CTT TCA ATA TAT ACC AAT GAT ACA ATA Lys Thr Ile Met Pro Phe Asp Leu Ser Ile Tyr Thr Asn Asp Thr Ile 835 840 845	2544
CTA ATA GAA ATG TTT AAT AAA TAT AAT AGC Leu Ile Glu Met Phe Asn Lys Tyr Asn Ser 850 855	2574

## (2) INFORMATION FOR SEQ ID NO: 22:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 858 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Met	Pro	Val	Thr	Ile	Asn	Asn	Phe	Asn	Tyr	Asn	Asp	Pro	Ile	Asp	Asn	1	5	10	15
Asn	Asn	Ile	Ile	Met	Met	Glu	Pro	Pro	Phe	Ala	Arg	Gly	Thr	Gly	Arg	20	25	30	
Tyr	Tyr	Lys	Ala	Phe	Lys	Ile	Thr	Asp	Arg	Ile	Trp	Ile	Ile	Pro	Glu	35	40	45	
Arg	Tyr	Thr	Phe	Gly	Tyr	Lys	Pro	Glu	Asp	Phe	Asn	Lys	Ser	Ser	Gly	50	55	60	
Ile	Phe	Asn	Arg	Asp	Val	Cys	Glu	Tyr	Tyr	Asp	Pro	Asp	Tyr	Leu	Asn	65	70	75	80
Thr	Asn	Asp	Lys	Lys	Asn	Ile	Phe	Leu	Gln	Thr	Met	Ile	Lys	Leu	Phe	85	90	95	
Asn	Arg	Ile	Lys	Ser	Lys	Pro	Leu	Gly	Glu	Lys	Leu	Leu	Glu	Met	Ile	100	105	110	
Ile	Asn	Gly	Ile	Pro	Tyr	Leu	Gly	Asp	Arg	Arg	Val	Pro	Leu	Glu	Glu	115	120	125	
Phe	Asn	Thr	Asn	Ile	Ala	Ser	Val	Thr	Val	Asn	Lys	Leu	Ile	Ser	Asn	130	135	140	
Pro	Gly	Glu	Val	Glu	Arg	Lys	Lys	Gly	Ile	Phe	Ala	Asn	Leu	Ile	Ile	145	150	155	160
Phe	Gly	Pro	Gly	Pro	Val	Leu	Asn	Glu	Asn	Glu	Thr	Ile	Asp	Ile	Gly	165	170	175	
Ile	Gln	Asn	His	Phe	Ala	Ser	Arg	Glu	Gly	Phe	Gly	Gly	Ile	Met	Gln	180	185	190	

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Met Lys Phe Cys Pro Glu Tyr Val Ser Val Phe Asn Asn Val Gln Glu  
 195 200 205  
 Asn Lys Gly Ala Ser Ile Phe Asn Arg Arg Gly Tyr Phe Ser Asp Pro  
 210 215 220  
 Ala Leu Ile Leu Met His Glu Leu Ile His Val Leu His Gly Leu Tyr  
 225 230 235 240  
 Gly Ile Lys Val Asp Asp Leu Pro Ile Val Pro Asn Glu Lys Lys Phe  
 245 250 255  
 Phe Met Gln Ser Thr Asp Ala Ile Gln Ala Glu Glu Leu Tyr Thr Phe  
 260 265 270  
 Gly Gly Gln Asp Pro Ser Ile Ile Thr Pro Ser Thr Asp Lys Ser Ile  
 275 280 285  
 Tyr Asp Lys Val Leu Gln Asn Phe Arg Gly Ile Val Asp Arg Leu Asn  
 290 295 300  
 Lys Val Leu Val Cys Ile Ser Asp Pro Asn Ile Asn Ile Asn Ile Tyr  
 305 310 315 320  
 Lys Asn Lys Phe Lys Asp Lys Tyr Lys Phe Val Glu Asp Ser Glu Gly  
 325 330 335  
 Lys Tyr Ser Ile Asp Val Glu Ser Phe Asp Lys Leu Tyr Lys Ser Leu  
 340 345 350  
 Met Phe Gly Phe Thr Glu Thr Asn Ile Ala Glu Asn Tyr Lys Ile Lys  
 355 360 365  
 Thr Arg Ala Ser Tyr Phe Ser Asp Ser Leu Pro Pro Val Lys Ile Lys  
 370 375 380  
 Asn Leu Leu Asp Asn Glu Ile Tyr Thr Ile Glu Glu Gly Phe Asn Ile  
 385 390 395 400  
 Ser Asp Lys Asp Met Glu Lys Glu Tyr Arg Gly Gln Asn Lys Ala Ile  
 405 410 415  
 Asn Lys Gln Ala Tyr Glu Glu Ile Ser Lys Glu His Leu Ala Val Tyr  
 420 425 430  
 Lys Ile Gln Met Cys Lys Ser Val Lys Ala Pro Gly Ile Cys Ile Asp  
 435 440 445  
 Val Asp Asn Glu Asp Leu Phe Phe Ile Ala Asp Lys Asn Ser Phe Ser  
 450 455 460  
 Asp Asp Leu Ser Lys Asn Glu Arg Ile Glu Tyr Asn Thr Gln Ser Asn  
 465 470 475 480  
 Tyr Ile Glu Asn Asp Phe Pro Ile Asn Glu Leu Ile Leu Asp Thr Asp  
 485 490 495  
 Leu Ile Ser Lys Ile Glu Leu Pro Ser Glu Asn Thr Glu Ser Leu Thr  
 500 505 510  
 Asp Phe Asn Val Asp Val Pro Val Tyr Glu Lys Gln Pro Ala Ile Lys  
 515 520 525  
 Lys Ile Phe Thr Asp Glu Asn Thr Ile Phe Gln Tyr Leu Tyr Ser Gln  
 530 535 540

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Thr Phe Pro Leu Asp Ile Arg Asp Ile Ser Leu Thr Ser Ser Phe Asp  
 545 550 555 560  
 Asp Ala Leu Leu Phe Ser Asn Lys Val Tyr Ser Phe Phe Ser Met Asp  
 565 570 575  
 Tyr Ile Lys Thr Ala Asn Lys Val Val Glu Ala Gly Leu Phe Ala Gly  
 580 585 590  
 Trp Val Lys Gln Ile Val Asn Asp Phe Val Ile Glu Ala Asn Lys Ser  
 595 600 605  
 Asn Thr Met Asp Lys Ile Ala Asp Ile Ser Leu Ile Val Pro Tyr Ile  
 610 615 620  
 Gly Leu Ala Leu Asn Val Gly Asn Glu Thr Ala Lys Gly Asn Phe Glu  
 625 630 635 640  
 Asn Ala Phe Glu Ile Ala Gly Ala Ser Ile Leu Leu Glu Phe Ile Pro  
 645 650 655  
 Glu Leu Leu Ile Pro Val Val Gly Ala Phe Leu Leu Glu Ser Tyr Ile  
 660 665 670  
 Asp Asn Lys Asn Lys Ile Ile Lys Thr Ile Asp Asn Ala Leu Thr Lys  
 675 680 685  
 Arg Asn Glu Lys Trp Ser Asp Met Tyr Gly Leu Ile Val Ala Gln Trp  
 690 695 700  
 Leu Ser Thr Val Asn Thr Gln Phe Tyr Thr Ile Lys Glu Gly Met Tyr  
 705 710 715 720  
 Lys Ala Leu Asn Tyr Gln Ala Gln Ala Leu Glu Glu Ile Ile Lys Tyr  
 725 730 735  
 Arg Tyr Asn Ile Tyr Ser Glu Lys Glu Lys Ser Asn Ile Asn Ile Asp  
 740 745 750  
 Phe Asn Asp Ile Asn Ser Lys Leu Asn Glu Gly Ile Asn Gln Ala Ile  
 755 760 765  
 Asp Asn Ile Asn Asn Phe Ile Asn Gly Cys Ser Val Ser Tyr Leu Met  
 770 775 780  
 Lys Lys Met Ile Pro Leu Ala Val Glu Lys Leu Leu Asp Phe Asp Asn  
 785 790 795 800  
 Thr Leu Lys Lys Asn Leu Leu Asn Tyr Ile Asp Glu Asn Lys Leu Tyr  
 805 810 815  
 Leu Ile Gly Ser Ala Glu Tyr Glu Lys Ser Lys Val Asn Lys Tyr Leu  
 820 825 830  
 Lys Thr Ile Met Pro Phe Asp Leu Ser Ile Tyr Thr Asn Asp Thr Ile  
 835 840 845  
 Leu Ile Glu Met Phe Asn Lys Tyr Asn Ser  
 850 855

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1644 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION:1..1644

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

ATG CCA GTT ACA ATA AAT AAT TTT AAT TAT AAT GAT CCT ATT GAT AAT	48
Met Pro Val Thr Ile Asn Asn Phe Asn Tyr Asn Asp Pro Ile Asp Asn	
1 5 10 15	
AAT AAT ATT ATT ATG ATG GAG CCT CCA TTT GCG AGA GGT ACG GGG AGA	96
Asn Asn Ile Ile Met Met Glu Pro Phe Ala Arg Gly Thr Gly Arg	
20 25 30	
TAT TAT AAA GCT TTT AAA ATC ACA GAT CGT ATT TGG ATA ATA CCG GAA	144
Tyr Tyr Lys Ala Phe Lys Ile Thr Asp Arg Ile Trp Ile Ile Pro Glu	
35 40 45	
AGA TAT ACT TTT GGA TAT AAA CCT GAG GAT TTT AAT AAA AGT TCC GGT	192
Arg Tyr Thr Phe Gly Tyr Lys Pro Glu Asp Phe Asn Lys Ser Ser Gly	
50 55 60	
ATT TTT AAT AGA GAT GTT TGT GAA TAT TAT GAT CCA GAT TAC TTA AAT	240
Ile Phe Asn Arg Asp Val Cys Glu Tyr Tyr Asp Pro Asp Tyr Leu Asn	
65 70 75 80	
ACT AAT GAT AAA AAG AAT ATA TTT TTA CAA ACA ATG ATC AAG TTA TTT	288
Thr Asn Asp Lys Lys Asn Ile Phe Leu Gln Thr Met Ile Lys Leu Phe	
85 90 95	
AAT AGA ATC AAA TCA AAA CCA TTG GGT GAA AAG TTA TTA GAG ATG ATT	336
Asn Arg Ile Lys Ser Lys Pro Leu Gly Glu Lys Leu Leu Glu Met Ile	
100 105 110	
ATA AAT GGT ATA CCT TAT CTT GGA GAT AGA CGT GTT CCA CTC GAA GAG	384
Ile Asn Gly Ile Pro Tyr Leu Gly Asp Arg Arg Val Pro Leu Glu Glu	
115 120 125	
TTT AAC ACA AAC ATT GCT AGT GTA ACT GTT AAT AAA TTA ATC AGT AAT	432
Phe Asn Thr Asn Ile Ala Ser Val Thr Val Asn Lys Leu Ile Ser Asn	
130 135 140	
CCA GGA GAA GTG GAG CGA AAA AAA GGT ATT TTC GCA AAT TTA ATA ATA	480
Pro Gly Glu Val Glu Arg Lys Lys Gly Ile Phe Ala Asn Leu Ile Ile	
145 150 155 160	
TTT GGA CCT GGG CCA GTT TTA AAT GAA AAT GAG ACT ATA GAT ATA GGT	528
Phe Gly Pro Gly Pro Val Leu Asn Glu Asn Glu Thr Ile Asp Ile Gly	
165 170 175	
ATA CAA AAT CAT TTT GCA TCA AGG GAA GGC TTC GGG GGT ATA ATG CAA	576
Ile Gln Asn His Phe Ala Ser Arg Glu Gly Phe Gly Gly Ile Met Gln	
180 185 190	
ATG AAG TTT TGC CCA GAA TAT GTA AGC GTA TTT AAT AAT GTT CAA GAA	624
Met Lys Phe Cys Pro Glu Tyr Val Ser Val Phe Asn Asn Val Gln Glu	
195 200 205	
AAC AAA GGC GCA AGT ATA TTT AAT AGA CGT GGA TAT TTT TCA GAT CCA	672
Asn Lys Gly Ala Ser Ile Phe Asn Arg Arg Gly Tyr Phe Ser Asp Pro	
210 215 220	

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GCC Ala 225	TTG Leu	ATA Ile	TTA Leu	ATG Met	CAT His 230	GAA Glu	CTT Leu	ATA Ile	CAT His 235	GTT Val	TTA Leu	CAT His	GGA Gly	TTA Leu	TAT Tyr 240	720
GGC Gly	ATT Ile	AAA Lys	GTA Val	GAT Asp 245	GAT Asp	TTA Leu	CCA Pro	ATT Ile	GTA Val 250	CCA Pro	AAT Asn	GAA Glu	AAA Lys	AAA Lys 255	TTT Phe	768
TTT Phe	ATG Met	CAA Gln	TCT Ser 260	ACA Thr	GAT Asp	GCT Ala	ATA Ile	CAG Gln 265	GCA Ala	GAA Glu	GAA Glu	CTA Leu	TAT Tyr 270	ACA Thr	TTT Phe	816
GGA Gly	GGA Gly	CAA Gln 275	GAT Asp	CCC Pro	AGC Ser	ATC Ile	ATA Ile 280	ACT Thr	CCT Pro	TCT Ser	ACG Thr	GAT Asp 285	AAA Lys	AGT Ser	ATC Ile	864
TAT Tyr 290	GAT Asp	AAA Lys	GTT Val	TTG Leu	CAA Gln	AAT Asn 295	TTT Phe	AGA Arg	GGG Gly	ATA Ile	GTT Val 300	GAT Asp	AGA Arg	CTT Leu	AAC Asn	912
AAG Lys 305	GTT Val	TTA Leu	GTT Val	TGC Cys 310	ATA Ile	TCA Ser	GAT Asp	CCT Pro	AAC Asn 315	ATT Ile	AAT Asn	ATT Ile	AAT Asn	ATA Ile	TAT Tyr 320	960
AAA Lys	AAT Asn	AAA Lys	TTT Phe	AAA Lys 325	GAT Asp	AAA Lys	TAT Tyr	AAA Lys	TTC Phe 330	GTT Val	GAA Glu	GAT Asp	TCT Ser	GAG Glu 335	GGA Gly	1008
AAA Lys	TAT Tyr	AGT Ser	ATA Ile 340	GAT Asp	GTA Val	GAA Glu	AGT Ser	TTT Phe 345	GAT Asp	AAA Lys	TTA Leu	TAT Tyr	AAA Lys 350	AGC Ser	TTA Leu	1056
ATG Met	TTT Phe 355	GGT Gly	TTT Phe	ACA Thr	GAA Glu	ACT Thr	AAT Asn 360	ATA Ile	GCA Ala	GAA Glu	AAT Asn	TAT Tyr 365	AAA Lys	ATA Ile	AAA Lys	1104
ACT Thr 370	AGA Arg	GCT Ala	TCT Ser	TAT Tyr	TTT Phe	AGT Ser 375	GAT Asp	TCC Ser	TTA Leu	CCA Pro	CCA Pro	GTA Val	AAA Lys	ATA Ile	AAA Lys	1152
AAT Asn 385	TTA Leu	TTA Leu	GAT Asp	AAT Asn	GAA Glu 390	ATC Ile	TAT Tyr	ACT Thr	ATA Ile	GAG Glu 395	GAA Glu	GGG Gly	TTT Phe	AAT Asn	ATA Ile 400	1200
TCT Ser	GAT Asp	AAA Lys	GAT Asp	ATG Met 405	GAA Glu	AAA Lys	GAA Glu	TAT Tyr	AGA Arg 410	GGT Gly	CAG Gln	AAT Asn	AAA Lys	GCT Ala 415	ATA Ile	1248
AAT Asn	AAA Lys	CAA Gln	GCT Ala 420	TAT Tyr	GAA Glu	GAA Glu	ATT Ile	AGC Ser	AAG Lys	GAG Glu	CAT His	TTG Leu	GCT Ala 430	GTA Val	TAT Tyr	1296
AAG Lys	ATA Ile	CAA Gln	ATG Met 435	TGT Cys	AAA Lys	AGT Ser	GTT Val	AAA Lys	GCT Ala	CCA Pro	GGA Gly	ATA Ile	TGT Cys	ATT Ile	GAT Asp	1344
GTT Val 450	GAT Asp	AAT Asn	GAA Glu	GAT Asp	TTG Leu	TTC Phe 455	TTT Phe	ATA Ile	GCT Ala	GAT Asp	AAA Lys 460	AAT Asn	AGT Ser	TTT Phe	TCA Ser	1392
GAT Asp 465	GAT Asp	TTA Leu	TCT Ser	AAA Lys	AAC Asn 470	GAA Glu	AGA Arg	ATA Ile	GAA Glu	TAT Tyr 475	AAT Asn	ACA Thr	CAG Gln	AGT Ser	AAT Asn 480	1440
TAT Tyr	ATA Ile	GAA Glu	AAT Asn	GAC Asp 485	TTC Phe	CCT Pro	ATA Ile	AAT Asn	GAA Glu 490	TTA Leu	ATT Ile	TTA Leu	GAT Asp	ACT Thr 495	GAT Asp	1488



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TTA ATA AGT AAA ATA GAA TTA CCA AGT GAA AAT ACA GAA TCA CTT ACT	1536
Leu Ile Ser Lys Ile Glu Leu Pro Ser Glu Asn Thr Glu Ser Leu Thr	
500 505 510	
GAT TTT AAT GTA GAT GTT CCA GTA TAT GAA AAA CAA CCC GCT ATA AAA	1584
Asp Phe Asn Val Asp Val Pro Val Tyr Glu Lys Gln Pro Ala Ile Lys	
515 520 525	
AAA ATT TTT ACA GAT GAA AAT ACC ATC TTT CAA TAT TTA TAC TCT CAG	1632
Lys Ile Phe Thr Asp Glu Asn Thr Ile Phe Gln Tyr Leu Tyr Ser Gln	
530 535 540	
ACA TTT CCT CTA	1644
Thr Phe Pro Leu	
545	

## (2) INFORMATION FOR SEQ ID NO: 24:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 548 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Met	Pro	Val	Thr	Ile	Asn	Asn	Phe	Asn	Tyr	Asn	Asp	Pro	Ile	Asp	Asn
1				5				10					15		
Asn	Asn	Ile	Ile	Met	Met	Glu	Pro	Pro	Phe	Ala	Arg	Gly	Thr	Gly	Arg
		20					25						30		
Tyr	Tyr	Lys	Ala	Phe	Lys	Ile	Thr	Asp	Arg	Ile	Trp	Ile	Ile	Pro	Glu
		35				40					45				
Arg	Tyr	Thr	Phe	Gly	Tyr	Lys	Pro	Glu	Asp	Phe	Asn	Lys	Ser	Ser	Gly
	50				55					60					
Ile	Phe	Asn	Arg	Asp	Val	Cys	Glu	Tyr	Tyr	Asp	Pro	Asp	Tyr	Leu	Asn
65			70					75						80	
Thr	Asn	Asp	Lys	Lys	Asn	Ile	Phe	Leu	Gln	Thr	Met	Ile	Lys	Leu	Phe
			85					90						95	
Asn	Arg	Ile	Lys	Ser	Lys	Pro	Leu	Gly	Glu	Lys	Leu	Leu	Glu	Met	Ile
		100					105					110			
Ile	Asn	Gly	Ile	Pro	Tyr	Leu	Gly	Asp	Arg	Arg	Val	Pro	Leu	Glu	Glu
	115					120					125				
Phe	Asn	Thr	Asn	Ile	Ala	Ser	Val	Thr	Val	Asn	Lys	Leu	Ile	Ser	Asn
	130				135					140					
Pro	Gly	Glu	Val	Glu	Arg	Lys	Lys	Gly	Ile	Phe	Ala	Asn	Leu	Ile	Ile
145			150						155					160	
Phe	Gly	Pro	Gly	Pro	Val	Leu	Asn	Glu	Asn	Glu	Thr	Ile	Asp	Ile	Gly
		165					170					175			
Ile	Gln	Asn	His	Phe	Ala	Ser	Arg	Glu	Gly	Phe	Gly	Gly	Ile	Met	Gln
	180						185					190			
Met	Lys	Phe	Cys	Pro	Glu	Tyr	Val	Ser	Val	Phe	Asn	Asn	Val	Gln	Glu
	195						200				205				

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Asn Lys Gly Ala Ser Ile Phe Asn Arg Arg Gly Tyr Phe Ser Asp Pro  
 210 215 220  
 Ala Leu Ile Leu Met His Glu Leu Ile His Val Leu His Gly Leu Tyr  
 225 230 235 240  
 Gly Ile Lys Val Asp Asp Leu Pro Ile Val Pro Asn Glu Lys Lys Phe  
 245 250 255  
 Phe Met Gln Ser Thr Asp Ala Ile Gln Ala Glu Glu Leu Tyr Thr Phe  
 260 265 270  
 Gly Gly Gln Asp Pro Ser Ile Ile Thr Pro Ser Thr Asp Lys Ser Ile  
 275 280 285  
 Tyr Asp Lys Val Leu Gln Asn Phe Arg Gly Ile Val Asp Arg Leu Asn  
 290 295 300  
 Lys Val Leu Val Cys Ile Ser Asp Pro Asn Ile Asn Ile Asn Ile Tyr  
 305 310 315 320  
 Lys Asn Lys Phe Lys Asp Lys Tyr Lys Phe Val Glu Asp Ser Glu Gly  
 325 330 335  
 Lys Tyr Ser Ile Asp Val Glu Ser Phe Asp Lys Leu Tyr Lys Ser Leu  
 340 345 350  
 Met Phe Gly Phe Thr Glu Thr Asn Ile Ala Glu Asn Tyr Lys Ile Lys  
 355 360 365  
 Thr Arg Ala Ser Tyr Phe Ser Asp Ser Leu Pro Pro Val Lys Ile Lys  
 370 375 380  
 Asn Leu Leu Asp Asn Glu Ile Tyr Thr Ile Glu Glu Gly Phe Asn Ile  
 385 390 395 400  
 Ser Asp Lys Asp Met Glu Lys Glu Tyr Arg Gly Gln Asn Lys Ala Ile  
 405 410 415  
 Asn Lys Gln Ala Tyr Glu Glu Ile Ser Lys Glu His Leu Ala Val Tyr  
 420 425 430  
 Lys Ile Gln Met Cys Lys Ser Val Lys Ala Pro Gly Ile Cys Ile Asp  
 435 440 445  
 Val Asp Asn Glu Asp Leu Phe Phe Ile Ala Asp Lys Asn Ser Phe Ser  
 450 455 460  
 Asp Asp Leu Ser Lys Asn Glu Arg Ile Glu Tyr Asn Thr Gln Ser Asn  
 465 470 475 480  
 Tyr Ile Glu Asn Asp Phe Pro Ile Asn Glu Leu Ile Leu Asp Thr Asp  
 485 490 495  
 Leu Ile Ser Lys Ile Glu Leu Pro Ser Glu Asn Thr Glu Ser Leu Thr  
 500 505 510  
 Asp Phe Asn Val Asp Val Pro Val Tyr Glu Lys Gln Pro Ala Ile Lys  
 515 520 525  
 Lys Ile Phe Thr Asp Glu Asn Thr Ile Phe Gln Tyr Leu Tyr Ser Gln  
 530 535 540  
 Thr Phe Pro Leu  
 545

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## (2) INFORMATION FOR SEQ ID NO: 25:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2616 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION:1..2616

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

ATG CAG TTC GTG AAC AAG CAG TTC AAC TAT AAG GAC CCT GTA AAC GGT	48
Met Gln Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly	
1 5 10 15	
GTT GAC ATT GCC TAC ATC AAA ATT CCA AAC GCC GGC CAG ATG CAG CCG	96
Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro	
20 25 30	
GTG AAG GCT TTC AAG ATT CAT AAC AAA ATC TGG GTT ATT CCG GAA CGC	144
Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg	
35 40 45	
GAT ACA TTT ACG AAC CCG GAA GAA GGA GAC TTG AAC CCG CCG CCG GAA	192
Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro Pro Glu	
50 55 60	
GCA AAG CAG GTG CCA GTT TCA TAC TAC GAT TCA ACC TAT CTG AGC ACA	240
Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr	
65 70 75 80	
GAC AAC GAG AAG GAT AAC TAC CTG AAG GGA GTG ACC AAA TTA TTC GAG	288
Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu	
85 90 95	
CGT ATT TAT TCC ACT GAC CTG GGC CGT ATG CTG CTG ACC TCA ATC GTC	336
Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val	
100 105 110	
CGC GGA ATC CCA TTT TGG GGT GGC AGT ACC ATT GAC ACG GAG TTG AAG	384
Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys	
115 120 125	
GTT ATT GAC ACT AAC TGC ATT AAC GTG ATC CAA CCA GAC GGT AGC TAC	432
Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr	
130 135 140	
AGA TCT GAA GAA CTT AAC CTC GTA ATC ATC GGG CCC TCC GCG GAC ATT	480
Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile	
145 150 155 160	
ATC CAG TTT GAG TGC AAG AGC TTT GGC CAC GAA GTG TTG AAC CTG ACG	528
Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr	
165 170 175	
CGT AAC GGT TAC GGC TCT ACT CAG TAC ATT CGT TTC AGC CCA GAC TTC	576
Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe	
180 185 190	

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ACG	TTC	GGT	TTC	GAG	GAG	AGC	CTG	GAG	GTT	GAT	ACC	AAC	CCG	CTG	TTG	624
Thr	Phe	Gly	Phe	Glu	Glu	Ser	Leu	Glu	Val	Asp	Thr	Asn	Pro	Leu	Leu	
		195					200					205				
GGT	GCA	GGC	AAG	TTC	GCA	ACT	GAT	CCA	GCG	GTG	ACC	CTG	GCA	CAC	GAG	672
Gly	Ala	Gly	Lys	Phe	Ala	Thr	Asp	Pro	Ala	Val	Thr	Leu	Ala	His	Glu	
	210					215					220					
CTG	ATC	CAC	GCC	GGT	CAT	CGT	CTG	TAT	GGC	ATT	GCG	ATT	AAC	CCG	AAC	720
Leu	Ile	His	Ala	Gly	His	Arg	Leu	Tyr	Gly	Ile	Ala	Ile	Asn	Pro	Asn	
225					230					235					240	
CGC	GTG	TTC	AAG	GTT	AAC	ACC	AAC	GCC	TAC	TAC	GAG	ATG	AGT	GGT	TTA	768
Arg	Val	Phe	Lys	Val	Asn	Thr	Asn	Ala	Tyr	Tyr	Glu	Met	Ser	Gly	Leu	
				245					250					255		
GAA	GTA	AGC	TTC	GAG	GAA	CTG	CGC	ACG	TTC	GGT	GGC	CAT	GAT	GCG	AAG	816
Glu	Val	Ser	Phe	Glu	Glu	Leu	Arg	Thr	Phe	Gly	Gly	His	Asp	Ala	Lys	
			260					265					270			
TTT	ATC	GAC	AGC	TTG	CAG	GAG	AAC	GAG	TTC	CGT	CTG	TAC	TAC	TAC	AAC	864
Phe	Ile	Asp	Ser	Leu	Gln	Glu	Asn	Glu	Phe	Arg	Leu	Tyr	Tyr	Tyr	Asn	
		275					280					285				
AAG	TTT	AAA	GAT	ATT	GCA	AGT	ACA	CTG	AAC	AAG	GCT	AAG	TCC	ATT	GTG	912
Lys	Phe	Lys	Asp	Ile	Ala	Ser	Thr	Leu	Asn	Lys	Ala	Lys	Ser	Ile	Val	
	290					295					300					
GGT	ACC	ACT	GCT	TCA	TTA	CAG	TAT	ATG	AAA	AAT	GTT	TTT	AAA	GAG	AAA	960
Gly	Thr	Thr	Ala	Ser	Leu	Gln	Tyr	Met	Lys	Asn	Val	Phe	Lys	Glu	Lys	
305					310					315					320	
TAT	CTC	CTA	TCT	GAA	GAT	ACA	TCT	GGA	AAA	TTT	TCG	GTA	GAT	AAA	TTA	1008
Tyr	Leu	Leu	Ser	Glu	Asp	Thr	Ser	Gly	Lys	Phe	Ser	Val	Asp	Lys	Leu	
				325					330					335		
AAA	TTT	GAT	AAG	TTA	TAC	AAA	ATG	TTA	ACA	GAG	ATT	TAC	ACA	GAG	GAT	1056
Lys	Phe	Asp	Lys	Leu	Tyr	Lys	Met	Leu	Thr	Glu	Ile	Tyr	Thr	Glu	Asp	
			340					345					350			
AAT	TTT	GTT	AAG	TTT	TTT	AAA	GTA	CTT	AAC	AGA	AAA	ACA	TAT	TTG	AAT	1104
Asn	Phe	Val	Lys	Phe	Phe	Lys	Val	Leu	Asn	Arg	Lys	Thr	Tyr	Leu	Asn	
		355					360					365				
TTT	GAT	AAA	GCC	GTA	TTT	AAG	ATA	AAT	ATA	GTA	CCT	AAG	GTA	AAT	TAC	1152
Phe	Asp	Lys	Ala	Val	Phe	Lys	Ile	Asn	Ile	Val	Pro	Lys	Val	Asn	Tyr	
	370					375					380					
ACA	ATA	TAT	GAT	GGA	TTT	AAT	TTA	AGA	AAT	ACA	AAT	TTA	GCA	GCA	AAC	1200
Thr	Ile	Tyr	Asp	Gly	Phe	Asn	Leu	Arg	Asn	Thr	Asn	Leu	Ala	Ala	Asn	
385					390					395					400	
TTT	AAT	GGT	CAA	AAT	ACA	GAA	ATT	AAT	AAT	ATG	AAT	TTT	ACT	AAA	CTA	1248
Phe	Asn	Gly	Gln	Asn	Thr	Glu	Ile	Asn	Asn	Met	Asn	Phe	Thr	Lys	Leu	
				405					410					415		
AAA	AAT	TTT	ACT	GGA	TTG	TTT	GAA	TTT	TAT	AAG	TTG	CTA	TGT	GTA	AGA	1296
Lys	Asn	Phe	Thr	Gly	Leu	Phe	Glu	Phe	Tyr	Lys	Leu	Leu	Cys	Val	Arg	
			420					425					430			
GGG	ATA	ATA	ACT	TCT	AAA	ACT	AAA	TCA	TTA	GAT	AAA	GGA	TAC	AAT	AAG	1344
Gly	Ile	Ile	Thr	Ser	Lys	Thr	Lys	Ser	Leu	Asp	Lys	Gly	Tyr	Asn	Lys	
		435					440					445				
GCA	TTA	AAT	GAT	TTA	TGT	ATC	AAA	GTT	AAT	AAT	TGG	GAC	TTG	TTT	TTT	1392
Ala	Leu	Asn	Asp	Leu	Cys	Ile	Lys	Val	Asn	Asn	Trp	Asp	Leu	Phe	Phe	
		450				455					460					

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AGT Ser 465	CCT Pro	TCA Ser	GAA Glu	GAT Asp	AAT Asn	TTT Phe	ACT Thr	AAT Asn	GAT Asp	CTA Leu	AAT Asn	AAA Lys	GGA Gly	GAA Glu	GAA Glu	1440
ATT Ile	ACA Thr	TCT Ser	GAT Asp	ACT Thr	AAT Asn	ATA Ile	GAA Glu	GCA Ala	GCA Ala	GAA Glu	GAA Glu	AAT Asn	ATT Ile	AGT Ser	TTA Leu	1488
GAT Asp	TTA Leu	ATA Ile	CAA Gln	CAA Gln	TAT Tyr	TAT Tyr	TTA Leu	ACC Phe	TTT Phe	AAT Asn	TTT Phe	GAT Asp	AAT Asn	GAA Glu	CCT Pro	1536
GAA Glu	AAT Asn	ATT Ile	TCA Ser	ATA Ile	GAA Glu	AAT Asn	CTT Leu	TCA Ser	AGT Ser	GAC Asp	ATT Ile	ATA Ile	GGC Gly	CAA Gln	TTA Leu	1584
GAA Glu	CTT Leu	ATG Met	CCT Pro	AAT Asn	ATA Ile	GAA Glu	AGA Arg	TTT Phe	CCT Pro	AAT Asn	GGA Gly	AAA Lys	AAG Lys	TAT Tyr	GAG Glu	1632
TTA Leu	GAT Asp	AAA Lys	TAT Tyr	ACT Thr	ATG Met	TTC Phe	CAT His	TAT Tyr	CTT Leu	CGT Arg	GCT Ala	CAA Gln	GAA Glu	TTT Phe	GAA Glu	1680
CAT His	GGT Gly	AAA Lys	TCT Ser	AGG Arg	ATT Ile	GCT Ala	TTA Leu	ACA Thr	AAT Asn	TCT Ser	GTT Val	AAC Asn	GAA Glu	GCA Ala	TTA Leu	1728
TTA Leu	AAT Asn	CCT Pro	AGT Ser	CGT Arg	GTT Val	TAT Tyr	ACA Thr	TTT Phe	TTT Phe	TCT Ser	TCA Ser	GAC Asp	TAT Tyr	GTA Val	AAG Lys	1776
AAA Lys	GTT Val	AAT Asn	AAA Lys	GCT Ala	ACG Thr	GAG Glu	GCA Ala	GCT Ala	ATG Met	TTT Phe	TTA Leu	GGC Gly	TGG Trp	GTA Val	GAA Glu	1824
CAA Gln	TTA Leu	GTA Val	TAT Tyr	GAT Asp	TTT Phe	ACC Thr	GAT Asp	GAA Glu	ACT Thr	AGC Ser	GAA Glu	GTA Val	AGT Ser	ACT Thr	ACG Thr	1872
GAT Asp	AAA Lys	ATT Ile	GCG Ala	GAT Asp	ATA Ile	ACT Thr	ATA Ile	ATT Ile	ATT Ile	CCA Pro	TAT Tyr	ATA Ile	GGA Gly	CCT Pro	GCT Ala	1920
TTA Leu	AAT Asn	ATA Ile	GGT Gly	AAT Asn	ATG Met	TTA Leu	TAT Tyr	AAA Lys	GAT Asp	GAT Asp	TTT Phe	GTA Val	GGT Gly	GCT Ala	TTA Leu	1968
ATA Ile	TTT Phe	TCA Ser	GGA Gly	GCT Ala	GTT Val	ATT Ile	CTG Leu	TTA Leu	GAA Glu	TTT Phe	ATA Ile	CCA Pro	GAG Glu	ATT Ile	GCA Ala	2016
ATA Ile	CCT Pro	GTA Val	TTA Leu	GGT Gly	ACT Thr	TTT Phe	GCA Ala	CTT Leu	GTA Val	TCA Ser	TAT Tyr	ATT Ile	GCG Ala	AAT Asn	AAG Lys	2064
GTT Val	CTA Leu	ACC Thr	GTT Val	CAA Gln	ACA Thr	ATA Ile	GAT Asp	AAT Asn	GCT Ala	TTA Leu	AGT Ser	AAA Lys	AGA Arg	AAT Asn	GAA Glu	2112
AAA Lys	TGG Trp	GAT Asp	GAG Glu	GTC Val	TAT Tyr	AAA Lys	TAT Tyr	ATA Ile	GTA Val	ACA Thr	AAT Asn	TGG Trp	TTA Leu	GCA Ala	AAG Lys	2160
GTT Val	AAT Asn	ACA Thr	CAG Gln	ATT Ile	GAT Asp	CTA Leu	ATA Ile	AGA Arg	AAA Lys	AAA Lys	ATG Met	AAA Lys	GAA Glu	GCT Ala	TTA Leu	2208

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GAA AAT CAA GCA GAA GCA ACA AAG GCT ATA ATA AAC TAT CAG TAT AAT Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn 740 745 750	2256
CAA TAT ACT GAG GAA GAG AAA AAT AAT ATT AAT TTT AAT ATT GAT GAT Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp 755 760 765	2304
TTA AGT TCG AAA CTT AAT GAG TCT ATA AAT AAA GCT ATG ATT AAT ATA Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile 770 775 780	2352
AAT AAA TTT TTG AAT CAA TGC TCT GTT TCA TAT TTA ATG AAT TCT ATG Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met 785 790 795 800	2400
ATC CCT TAT GGT GTT AAA CGG TTA GAA GAT TTT GAT GCT AGT CTT AAA Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys 805 810 815	2448
GAT GCA TTA TTA AAG TAT ATA TAT GAT AAT AGA GGA ACT TTA ATT GGT Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly 820 825 830	2496
CAA GTA GAT AGA TTA AAA GAT AAA GTT AAT AAT ACA CTT AGT ACA GAT Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp 835 840 845	2544
ATA CCT TTT CAG CTT TCC AAA TAC GTA GAT AAT CAA AGA TTA TTA TCT Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser 850 855 860	2592
ACA TTT ACT GAA TAT ATT AAG TAA Thr Phe Thr Glu Tyr Ile Lys * 865 870	2616

## (2) INFORMATION FOR SEQ ID NO: 26:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 872 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Met	Gln	Phe	Val	Asn	Lys	Gln	Phe	Asn	Tyr	Lys	Asp	Pro	Val	Asn	Gly	1	5	10	15
Val	Asp	Ile	Ala	Tyr	Ile	Lys	Ile	Pro	Asn	Ala	Gly	Gln	Met	Gln	Pro	20	25	30	
Val	Lys	Ala	Phe	Lys	Ile	His	Asn	Lys	Ile	Trp	Val	Ile	Pro	Glu	Arg	35	40	45	
Asp	Thr	Phe	Thr	Asn	Pro	Glu	Glu	Gly	Asp	Leu	Asn	Pro	Pro	Pro	Glu	50	55	60	
Ala	Lys	Gln	Val	Pro	Val	Ser	Tyr	Tyr	Asp	Ser	Thr	Tyr	Leu	Ser	Thr	65	70	75	80
Asp	Asn	Glu	Lys	Asp	Asn	Tyr	Leu	Lys	Gly	Val	Thr	Lys	Leu	Phe	Glu	85	90	95	
Arg	Ile	Tyr	Ser	Thr	Asp	Leu	Gly	Arg	Met	Leu	Leu	Thr	Ser	Ile	Val	100	105	110	

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Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys  
 115 120 125  
 Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr  
 130 135 140  
 Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile  
 145 150 155 160  
 Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr  
 165 170 175  
 Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe  
 180 185 190  
 Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu  
 195 200 205  
 Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu  
 210 215 220  
 Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn  
 225 230 235 240  
 Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu  
 245 250 255  
 Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys  
 260 265 270  
 Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn  
 275 280 285  
 Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser Ile Val  
 290 295 300  
 Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys Glu Lys  
 305 310 315 320  
 Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp Lys Leu  
 325 330 335  
 Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr Glu Asp  
 340 345 350  
 Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr Leu Asn  
 355 360 365  
 Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val Asn Tyr  
 370 375 380  
 Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala Ala Asn  
 385 390 395 400  
 Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr Lys Leu  
 405 410 415  
 Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys Val Arg  
 420 425 430  
 Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Asp Lys Gly Tyr Asn Lys  
 435 440 445  
 Ala Leu Asn Asp Leu Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe  
 450 455 460

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Ser	Pro	Ser	Glu	Asp	Asn	Phe	Thr	Asn	Asp	Leu	Asn	Lys	Gly	Glu	Glu	465	470	475	480
Ile	Thr	Ser	Asp	Thr	Asn	Ile	Glu	Ala	Ala	Glu	Glu	Asn	Ile	Ser	Leu	485	490	495	
Asp	Leu	Ile	Gln	Gln	Tyr	Tyr	Leu	Thr	Phe	Asn	Phe	Asp	Asn	Glu	Pro	500	505	510	
Glu	Asn	Ile	Ser	Ile	Glu	Asn	Leu	Ser	Ser	Asp	Ile	Ile	Gly	Gln	Leu	515	520	525	
Glu	Leu	Met	Pro	Asn	Ile	Glu	Arg	Phe	Pro	Asn	Gly	Lys	Lys	Tyr	Glu	530	535	540	
Leu	Asp	Lys	Tyr	Thr	Met	Phe	His	Tyr	Leu	Arg	Ala	Gln	Glu	Phe	Glu	545	550	555	560
His	Gly	Lys	Ser	Arg	Ile	Ala	Leu	Thr	Asn	Ser	Val	Asn	Glu	Ala	Leu	565	570	575	
Leu	Asn	Pro	Ser	Arg	Val	Tyr	Thr	Phe	Phe	Ser	Ser	Asp	Tyr	Val	Lys	580	585	590	
Lys	Val	Asn	Lys	Ala	Thr	Glu	Ala	Ala	Met	Phe	Leu	Gly	Trp	Val	Glu	595	600	605	
Gln	Leu	Val	Tyr	Asp	Phe	Thr	Asp	Glu	Thr	Ser	Glu	Val	Ser	Thr	Thr	610	615	620	
Asp	Lys	Ile	Ala	Asp	Ile	Thr	Ile	Ile	Ile	Pro	Tyr	Ile	Gly	Pro	Ala	625	630	635	640
Leu	Asn	Ile	Gly	Asn	Met	Leu	Tyr	Lys	Asp	Asp	Phe	Val	Gly	Ala	Leu	645	650	655	
Ile	Phe	Ser	Gly	Ala	Val	Ile	Leu	Leu	Glu	Phe	Ile	Pro	Glu	Ile	Ala	660	665	670	
Ile	Pro	Val	Leu	Gly	Thr	Phe	Ala	Leu	Val	Ser	Tyr	Ile	Ala	Asn	Lys	675	680	685	
Val	Leu	Thr	Val	Gln	Thr	Ile	Asp	Asn	Ala	Leu	Ser	Lys	Arg	Asn	Glu	690	695	700	
Lys	Trp	Asp	Glu	Val	Tyr	Lys	Tyr	Ile	Val	Thr	Asn	Trp	Leu	Ala	Lys	705	710	715	720
Val	Asn	Thr	Gln	Ile	Asp	Leu	Ile	Arg	Lys	Lys	Met	Lys	Glu	Ala	Leu	725	730	735	
Glu	Asn	Gln	Ala	Glu	Ala	Thr	Lys	Ala	Ile	Ile	Asn	Tyr	Gln	Tyr	Asn	740	745	750	
Gln	Tyr	Thr	Glu	Glu	Glu	Lys	Asn	Asn	Ile	Asn	Phe	Asn	Ile	Asp	Asp	755	760	765	
Leu	Ser	Ser	Lys	Leu	Asn	Glu	Ser	Ile	Asn	Lys	Ala	Met	Ile	Asn	Ile	770	775	780	
Asn	Lys	Phe	Leu	Asn	Gln	Cys	Ser	Val	Ser	Tyr	Leu	Met	Asn	Ser	Met	785	790	795	800
Ile	Pro	Tyr	Gly	Val	Lys	Arg	Leu	Glu	Asp	Phe	Asp	Ala	Ser	Leu	Lys	805	810	815	



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Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly  
                   820                                  825                                  830

Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp  
                   835                                  840                                  845

Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser  
                   850                                  855                                  860

Thr Phe Thr Glu Tyr Ile Lys \*  
                   865                                  870

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2574 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

ATGCCGGTTA CCATCAACAA CTTCAACTAC AACGACCCGA TCGACAACAA CAACATCATC	60
ATGATGGAAC CGCCGTTTCGC ACGTGGTACC GGTCGTTACT ACAAGGCTTT CAAGATCACC	120
GACCGTATCT GGATCATCCC GGAACGTTAC ACCTTCGGTT ACAAACCTGA GGA CTTC AAC	180
AAGAGTAGCG GGATTTTCAA TCGTGACGTC TGCGAGTACT ATGATCCAGA TTATCTGAAT	240
ACCAACGATA AGAAGAACAT ATTCCCTTCAG ACTATGATCA AGTTATTTAA TAGAATCAAA	300
TCAAAACCAT TGGGTGAAAA GTTATTAGAG ATGATTATAA ATGGTATACC TTATCTTGGA	360
GATAGACGTG TTCCACTCGA AGAGTTTAAAC ACAAACATTG CTAGTGTAAC TGTTAATAAA	420
TTAATCAGTA ATCCAGGAGA AGTGGAGCGA AAAAAAGGTA TTTTCGCAA TTTAATAATA	480
TTTGGACCTG GGCCAGTTTT AAATGAAAAT GAGACTATAG ATATAGGTAT ACAAATCAT	540
TTTGCATCAA GGGAAGGCTT CGGGGGTATA ATGCAAATGA AGTTTTGCCC AGAATATGTA	600
AGCGTATTTA ATAATGTTCA AGAAAACAAA GGCGCAAGTA TATTTAATAG ACGTGGATAT	660
TTTTCAGATC CAGCCTTGAT ATTAATGCAT GAACTTATAC ATGTTTTACA TGGATTATAT	720
GGCATTAAAG TAGATGATTT ACCAATTGTA CCAAATGAAA AAAAATTTTT TATGCAATCT	780
ACAGATGCTA TACAGGCAGA AGAACTATAT ACATTTGGAG GACAAGATCC CAGCATCATA	840
ACTCCTTCTA CGGATAAAAG TATCTATGAT AAAGTTTTCG AAAATTTT TAG AGGGATAGTT	900
GATAGACTTA ACAAGGTTTT AGTTTGCATA TCAGATCCTA ACATTAATAT TAATATATAT	960
AAAAATAAAT TTAAAGATAA ATATAAATTC GTTGAAGATT CTGAGGGAAA ATATAGTATA	1020
GATGTAGAAA GTTTTGATAA ATTATATAAA AGCTTAATGT TTGGTTTTAC AGAACTAAT	1080
ATAGCAGAAA ATTATAAAAT AAAA ACTAGA GCTTCTTATT TTAGTGATTC CTTACCACCA	1140
GTAAAAATAA AAAATTTATT AGATAATGAA ATCTATACTA TAGAGGAAGG GTTTAATATA	1200

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TCTGATAAAG ATATGGAAAA AGAATATAGA GGTCAGAATA AAGCTATAAA TAAACAAGCT	1260
TATGAAGAAA TTAGCAAGGA GCATTTGGCT GTATATAAGA TACAAATGTG TAAAAGTGTT	1320
AAAGCTCCAG GAATATGTAT TGATGTTGAT AATGAAGATT TGTTCTTTAT AGCTGATAAA	1380
AATAGTTTTT CAGATGATTT ATCTAAAAAC GAAAGAATAG AATATAATAC ACAGAGTAAT	1440
TATATAGAAA ATGACTTCCC TATAAATGAA TTAATTTTAG ATACTGATTT AATAAGTAAA	1500
ATAGAATTAC CAAGTGAAAA TACAGAATCA CTTACTGATT TTAATGTAGA TGTTCAGTA	1560
TATGAAAAAC AACCCGCTAT AAAAAAATT TTTACAGATG AAAATACCAT CTTTCAATAT	1620
TTATACTCTC AGACATTTCC TCTAGATATA AGAGATATAA GTTTAACATC TTCATTTGAT	1680
GATGCATTAT TATTTTCTAA CAAAGTTTAT TCATTTTTTT CTATGGATTA TATTAAACT	1740
GCTAATAAAG TGGTAGAAGC AGGATTATTT GCAGGTTGGG TGAAACAGAT AGTAAATGAT	1800
TTTGTAATCG AAGCTAATAA AAGCAATACT ATGGATAAAA TTGCAGATAT ATCTCTAATT	1860
GTCCTTTATA TAGGATTAGC TTAAATGTA GGAAATGAAA CAGCTAAAGG AAATTTTGAA	1920
AATGCTTTTG AGATTGCAGG AGCCAGTATT CTACTAGAAT TTATACCAGA ACTTTTAATA	1980
CCTGTAGTTG GAGCCTTTTT ATTAGAATCA TATATTGACA ATAAAAATAA AATTATTAAA	2040
ACAATAGATA ATGCTTTAAC TAAAGAAAT GAAAAATGGA GTGATATGTA CGGATTAATA	2100
GTAGCGCAAT GGCTCTCAAC AGTTAATACT CAATTTTATA CAATAAAAGA GGGAATGTAT	2160
AAGGCTTTAA ATTATCAAGC ACAAGCATTG GAAGAAATAA TAAATACAG ATATAATATA	2220
TATTCTGAAA AAGAAAAGTC AAATATTAAC ATCGATTTTA ATGATATAAA TTCTAAACTT	2280
AATGAGGGTA TTAACCAAGC TATAGATAAT ATAAATAATT TTATAAATGG ATGTTCTGTA	2340
TCATATTTAA TGAAAAAAT GATTCCATTA GCTGTAGAAA AATTACTAGA CTTTGATAAT	2400
ACTCTCAAAA AAAATTTGTT AAATTATATA GATGAAAATA AATTATATTT GATTGGAAGT	2460
GCAGAATATG AAAAATCAAA AGTAAATAAA TACTTGAAAA CCATTATGCC GTTTGATCTT	2520
TCAATATATA CCAATGATAC AATACTAATA GAAATGTTTA ATAAATATAA TAGC	2574

## (2) INFORMATION FOR SEQ ID NO: 28:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2574 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

ATGCCAGTTA CAATAAATAA TTTTAATTAT AATGATCCTA TTGATAATAA TAATATTATT	60
ATGATGGAGC CTCCATTTGC GAGAGGTACG GGGAGATATT ATAAAGCTTT TAAATCACA	120
GATCGTATTT GGATAATACC GGAAAGATAT ACTTTTGGAT ATAAACCTGA GGATTTTAAT	180
AAAAGTCCG GTATTTTAA TAGAGATGTT TGTGAATATT ATGATCCAGA TTAATTAAAT	240

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ACTAATGATA AAAAGAATAT ATTTTTACAA ACAATGATCA AGTTATTTAA TAGAATCAAA	300
TCAAAACCAT TGGGTGAAAA GTTATTAGAG ATGATTATAA ATGGTATACC TTATCTTGGA	360
GATAGACGTG TTCCACTCGA AGAGTTTAAC ACAAACATTG CTAGTGTAAC TGTTAATAAA	420
TTAATCAGTA ATCCAGGAGA AGTGGAGCGA AAAAAAGGTA TTTTCGCAAA TTTAATAATA	480
TTTGGACCTG GGCCAGTTTT AAATGAAAAT GAGACTATAG ATATAGGTAT ACAAATCAT	540
TTTGCATCAA GGAAGGCTT CGGGGGTATA ATGCAAATGA AGTTTTGCCC AGAATATGTA	600
AGCGTATTTA ATAATGTTCA AGAAAACAAA GCGCAAGTA TATTTAATAG ACGTGGATAT	660
TTTTCAGATC CAGCCTTGAT ATTAATGCAT GAACTCATCC ACGTCCTCCA CGGTCTCTAC	720
GGTATCAAAG TAGACGACCT CCCGATCGTC CCGAACGAAA AAAAATTCTT CATGCAGAGC	780
ACCGACGCAA TCCAGGCAGA AGAACTCTAC ACCTTCGGTG GTCAGGACCC GAGCATCATC	840
ACCCCGAGCA CCGACAAAAG CATCTACGAC AAAGTCCTCC AGAACTTCCG TGGTATCGTC	900
GACCGTCTCA ACAAAGTCCT CGTCTGCATC AGCGACCCGA ACATCAACAT CAACATCTAC	960
AAAAACAAAT TCAAAGACAA ATACAAATTC GTCGAAGACA GCGAAGGTAA ATACAGCATC	1020
GACGTCGAGA GCTTCGACAA ACTCTACAAA AGCCTCATGT TCGGTTTCAC CGAAACCAAC	1080
ATCGCAGAAA ACTACAAAAT CAAAACCCGT GCAAGCTACT TCAGCGACAG CCTCCCGCCG	1140
GTCAAATCA AAAACCTCCT CGACAACGAA ATCTACACCA TCGAAGAAGG TTTCAACATC	1200
AGCGACAAAG ACATGGAAAA AGAATACCGT GGTCAGAACA AAGCAATCAA CAAACAAGCT	1260
TACGAAGAAA TCAGCAAAGA ACACCTCGCA GTCTACAAAA TCCAGATGTG CAAAAGCGTC	1320
AAAGCACCGG GTATCTGCAT CGACGTTGAC AACGAAGACC TCTTCTTCAT CGCAGACAAA	1380
AACAGCTTCA GCGACGACCT CAGCAAAAAC GAACGTATCG AATACAACAC CCAGAGCAAC	1440
TACATCGAAA ACGACTTCCC GATCAACGAA CTCATCCTCG ACACCGACCT CATCAGCAAA	1500
ATCGAACTCC CGAGCGAAAA CACCGAAAGC CTCACCGACT TCAACGTTGA CGTCCCGGTC	1560
TACGAAAAAC AGCCGGCAAT CAAAAAATC TTCACCGACG AAAACACCAT CTTCCAGTAC	1620
CTCTACAGCC AGACCTTCCC GCTAGATATA AGAGATATAA GTTTAACATC TTCATTTGAT	1680
GATGCATTAT TATTTTCTAA CAAAGTTTAT TCATTTTTTT CTATGGATTA TATTAAACT	1740
GCTAATAAAG TGGTAGAAGC AGGATTATTT GCAGGTTGGG TGAAACAGAT AGTAAATGAT	1800
TTTGTAAATCG AAGCTAATAA AAGCAATACT ATGGATAAAA TTGCAGATAT ATCTCTAATT	1860
GTTCCTTATA TAGGATTAGC TTAAATGTA GGAAATGAAA CAGCTAAAGG AAATTTTGAA	1920
AATGCTTTTG AGATTGCAGG AGCCAGTATT CTACTAGAAT TTATACCAGA ACTTTTAATA	1980
CCTGTAGTTG GAGCCTTTTT ATTAGAATCA TATATTGACA ATAAAAATAA AATTATTAAA	2040
ACAATAGATA ATGCTTTAAC TAAAGAAAT GAAAAATGGA GTGATATGTA CGGATTAATA	2100
GTAGCGCAAT GGCTCTCAAC AGTTAATACT CAATTTTATA CAATAAAAGA GGAATGTAT	2160
AAGGCTTTAA ATTATCAAGC ACAAGCATTG GAAGAAATAA TAAAATACAG ATATAATATA	2220
TATTCTGAAA AAGAAAAGTC AAATATTAAC ATCGATTTTA ATGATATAAA TTCTAACTT	2280

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AATGAGGGTA TTAACCAAGC TATAGATAAT ATAAATAATT TTATAAATGG ATGTTCTGTA	2340
TCATATTTAA TGAAAAAAT GATTCCATTA GCTGTAGAAA AATTACTAGA CTTTGATAAT	2400
ACTCTCAAAA AAAATTTGTT AAATTATATA GATGAAAATA AATTATATTT GATTGGAAGT	2460
GCAGAATATG AAAAATCAAA AGTAAATAAA TACTTGAAAA CCATTATGCC GTTTGATCTT	2520
TCAATATATA CCAATGATAC AATACTAATA GAAATGTTTA ATAAATATAA TAGC	2574

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**CLAIMS**

1. A polypeptide comprising first and second domains, wherein said first domain is adapted to cleave one or more vesicle or plasma-membrane associated proteins essential to exocytosis, and wherein said second domain is adapted (i) to translocate the polypeptide into a cell or (ii) to increase the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both to translocate the polypeptide into a cell and to increase the solubility of the polypeptide compared to the solubility of the first domain on its own, said polypeptide being free of clostridial neurotoxin and free of clostridial neurotoxin precursor that can be converted into toxin by proteolytic action.
2. A polypeptide according to Claim 1 wherein said first domain comprises a clostridial toxin light chain.
3. A polypeptide according to Claim 1 wherein said first domain comprises a fragment or variant of a clostridial toxin light chain.
4. A polypeptide according to Claim 2 or 3 wherein the clostridial toxin is a botulinum toxin.
5. A polypeptide according to any preceding claim wherein the first domain exhibits endopeptidase activity specific for a substrate selected from one or more of SNAP-25, synaptobrevin/VAMP and syntaxin.
6. A polypeptide according to any preceding claim wherein said second domain comprises a clostridial toxin heavy chain H<sub>N</sub> portion.
7. A polypeptide according to any of Claims 1-5 wherein said second domain comprises a fragment or variant of a clostridial toxin heavy chain H<sub>N</sub> portion.
8. A polypeptide according to Claim 6 or 7 wherein the clostridial toxin is a

botulinum toxin.

9. A polypeptide according to any of Claims 1-8 further comprising a third domain adapted for binding of the polypeptide to a cell, by binding of the third domain directly to a cell or by binding of the third domain to a ligand or to ligands that bind to a cell.

10. A polypeptide according to Claim 9 wherein said third domain is for binding the polypeptide to an immunoglobulin.

11. A polypeptide according to Claim 10 wherein said third domain is a tandem repeat synthetic IgG binding domain derived from domain  $\beta$  of Staphylococcal protein A.

12. A polypeptide according to Claim 9 wherein said third domain comprises an amino acid sequence that binds to a cell surface receptor.

13. A polypeptide according to Claim 12 wherein said third domain is insulin-like growth factor-1 (IGF-1).

14. A polypeptide according to any preceding claim comprising a botulinum toxin light chain or a fragment or a variant of a botulinum toxin light chain and a portion designated  $H_N$  of a botulinum toxin heavy chain.

15. A polypeptide according to Claim 14 wherein one or both of (a) the toxin light chain or fragment or variant of toxin light chain and (b) the portion of the toxin heavy chain are of botulinum toxin type A.

16. A polypeptide according to Claim 15 wherein the botulinum toxin type A light chain variant has at residue 2 a glutamate, at residue 26 a lysine and at residue 27 a tyrosine.

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17. A polypeptide according to Claim 14 wherein one or both of (a) the toxin light chain or fragment or variant of toxin light chain and (b) the portion of the toxin heavy chain are of botulinum toxin type B.
18. A polypeptide according to any of Claims 1-13 comprising a botulinum toxin light chain or a fragment or a variant of a botulinum toxin light chain and at least 100 N-terminal amino acids of a botulinum toxin heavy chain.
19. A polypeptide according to Claim 18 comprising a botulinum toxin type B light chain, or a fragment or variant thereof, and 107 N-terminal amino acids of a botulinum toxin type B heavy chain.
20. A polypeptide according to Claim 15 or 16 comprising at least 423 of the N-terminal amino acids of botulinum toxin type A heavy chain.
21. A polypeptide according to Claim 20 comprising a botulinum toxin type A light chain and 423 N-terminal amino acids of a botulinum toxin type A heavy chain.
22. A polypeptide according to Claim 20 comprising a botulinum toxin type A light chain variant wherein residue 2 is a glutamate, residue 26 is a lysine and residue 27 is a tyrosine, and 423 N-terminal amino acids of a botulinum toxin type A heavy chain.
23. A polypeptide according to Claim 17 comprising at least 417 of the N-terminal amino acids of botulinum toxin type B heavy chain.
24. A polypeptide according to Claim 23 comprising a botulinum toxin type B light chain and 417 N-terminal amino acids of a botulinum toxin type B heavy chain.
25. A polypeptide according to any of Claims 14-24 lacking a portion designated

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H<sub>C</sub> of a botulinum toxin heavy chain.

26. A polypeptide comprising a botulinum toxin light chain and a fragment of a botulinum toxin heavy chain, said fragment being not capable of binding to cell surface receptors.

27. A polypeptide according to Claim 26 lacking an intact portion designated H<sub>C</sub> of a botulinum toxin heavy chain.

28. A polypeptide according to any preceding claim comprising a variant of a clostridial toxin and further comprising a site for cleavage by a proteolytic enzyme, which cleavage site is not present in the native toxin.

29. A polypeptide according to Claim 28 comprising a variant of a clostridial toxin light chain and further comprising a site for cleavage by a proteolytic enzyme, which cleavage site is not present in the native toxin light chain.

30. A polypeptide according to Claim 28 or 29 comprising a variant of a clostridial toxin heavy chain H<sub>N</sub> portion and further comprising a site for cleavage by a proteolytic enzyme, which cleavage site is not present in the native toxin heavy chain H<sub>N</sub> portion.

31. A polypeptide according to Claim 28, 29 or 30 obtainable by modification of a DNA encoding the polypeptide so as to introduce one or more nucleotides coding for the cleavage site.

32. A fusion protein comprising a fusion of (a) a polypeptide according to any of Claims 1-31 with (b) a second polypeptide being a polypeptide or oligopeptide adapted for binding to an affinity matrix so as to enable purification of the fusion protein using said matrix.

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33. A fusion protein according to Claim 32 wherein said second polypeptide is



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adapted to bind to a chromatography column, such as an affinity matrix of glutathione Sepharose.

34. A fusion protein according to Claim 32 or 33 wherein a specific protease cleavage site is incorporated between the first and second polypeptides, said protease site enabling proteolytic separation of first and second polypeptides.

35. A composition comprising a derivative of a clostridial toxin, said derivative retaining at least 10% of the endopeptidase activity of the botulinum toxin, said derivative further being non-toxic *in vivo* due to its inability to bind to cell surface receptors, and wherein the composition is free of any component, such as toxin or a further toxin derivative, that is toxic *in vivo*.

36. A composition according to Claim 35 or a polypeptide according to any of Claims 1-31 or a fusion protein according to Claim 32, 33 or 34 for use as a positive control in a toxin assay.

37. A composition according to Claim 35 or a polypeptide according to any of Claims 1-31 or a fusion protein according to Claim 32, 33 or 34 for use as a vaccine against clostridial toxin.

38. A composition according to Claim 35 or a polypeptide according to any of Claims 1-31 or a fusion protein according to Claim 32, 33 or 34 for *in vivo* use.

39. A pharmaceutical composition comprising a composition according to Claim 35, a polypeptide according to any of claims 1-31 or a fusion protein according to Claim 32, 33 or 34, in combination with a pharmaceutically acceptable carrier.

40. A nucleic acid encoding a polypeptide or a fusion protein according to any of Claims 1-34.

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41. A nucleic acid encoding a polypeptide or a fusion protein according to Claim

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40 and comprising nucleotides encoding residues 1-448 of a botulinum toxin type A light chain.

42. A nucleic acid according to Claim 40 or 41 comprising nucleotides encoding residues 1-423 of a botulinum toxin type A heavy chain H<sub>N</sub> domain.

43. A nucleic acid encoding a polypeptide or a fusion protein according to Claim 40 and comprising nucleotides encoding residues 1-470 of a botulinum toxin type B light chain.

44. A nucleic acid encoding a polypeptide or a fusion protein according to Claim 40 or 43 comprising nucleotides encoding residues 1-417 of a botulinum toxin type B heavy chain H<sub>N</sub> domain.

45. A nucleic acid according to any of Claims 40-44 comprising nucleotides encoding a restriction endonuclease cleavage site not present in native clostridial toxin sequence.

46. A nucleotide according to Claim 45 obtainable by modification of a nucleotide encoding a polypeptide or fusion protein according to any of claims 1-34 so as to introduce said cleavage site.

47. A DNA according to any of claims 40-46.

48. A DNA selected from SEQ ID No:s 1, 8, 10, 12, 14, 16, 18, 23 and 24.

49. A method of manufacture of a polypeptide according to any of Claims 1-31 comprising expressing in a host cell a nucleic acid according to any of Claims 40-48 and recovering the polypeptide.

50. A method of manufacture of a polypeptide according to any of Claims 1-31 comprising expressing in a host cell a nucleic acid encoding a fusion protein

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according to Claim 32, 33 or 34, purifying the fusion protein by eluting the fusion protein through an affinity matrix adapted to retain the fusion protein and eluting through said matrix a ligand adapted to displace the fusion protein, and recovering the fusion protein.

51. A method of manufacture according to Claims 49 or 50 in which the nucleic acid is DNA.

52. A cell expressing a polypeptide or fusion protein according to any of Claims 1-34.

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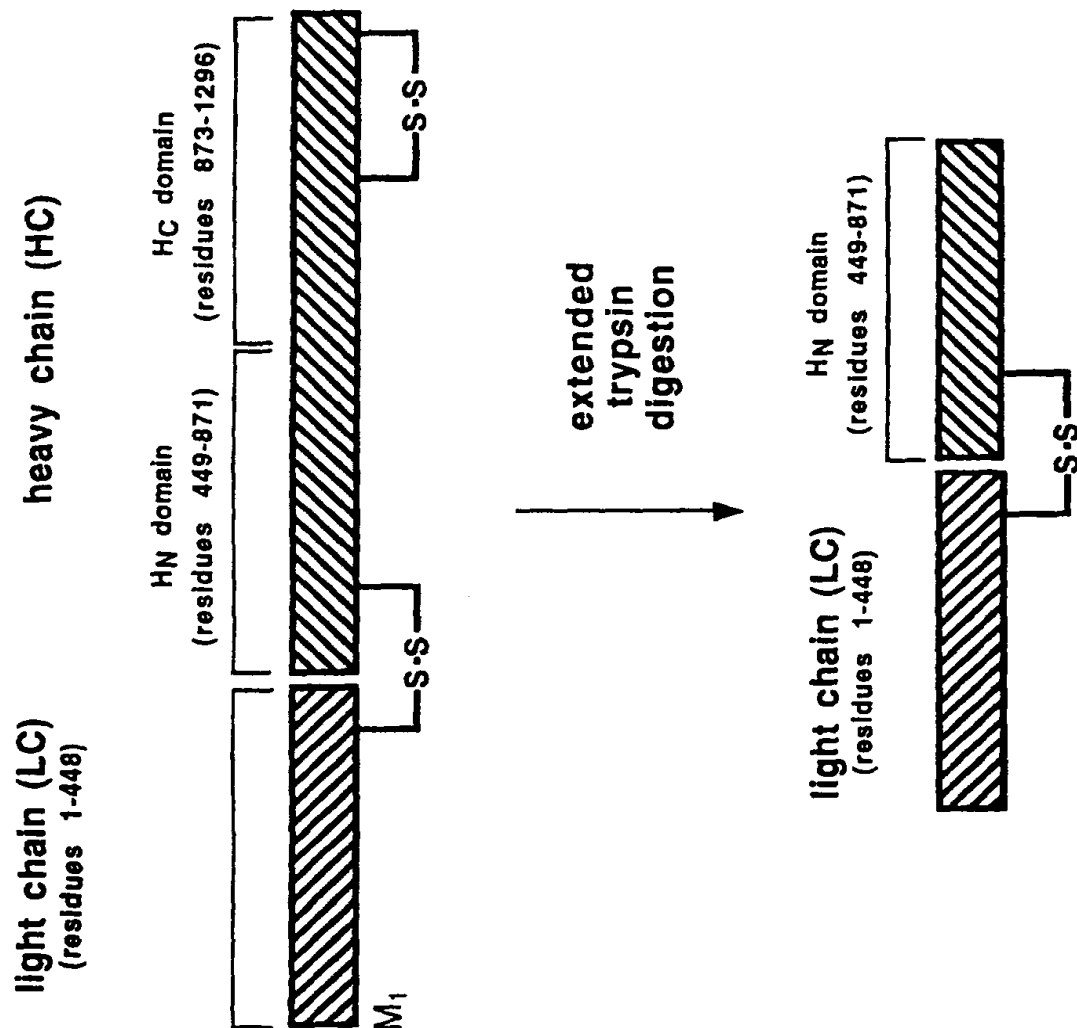


FIG. 1

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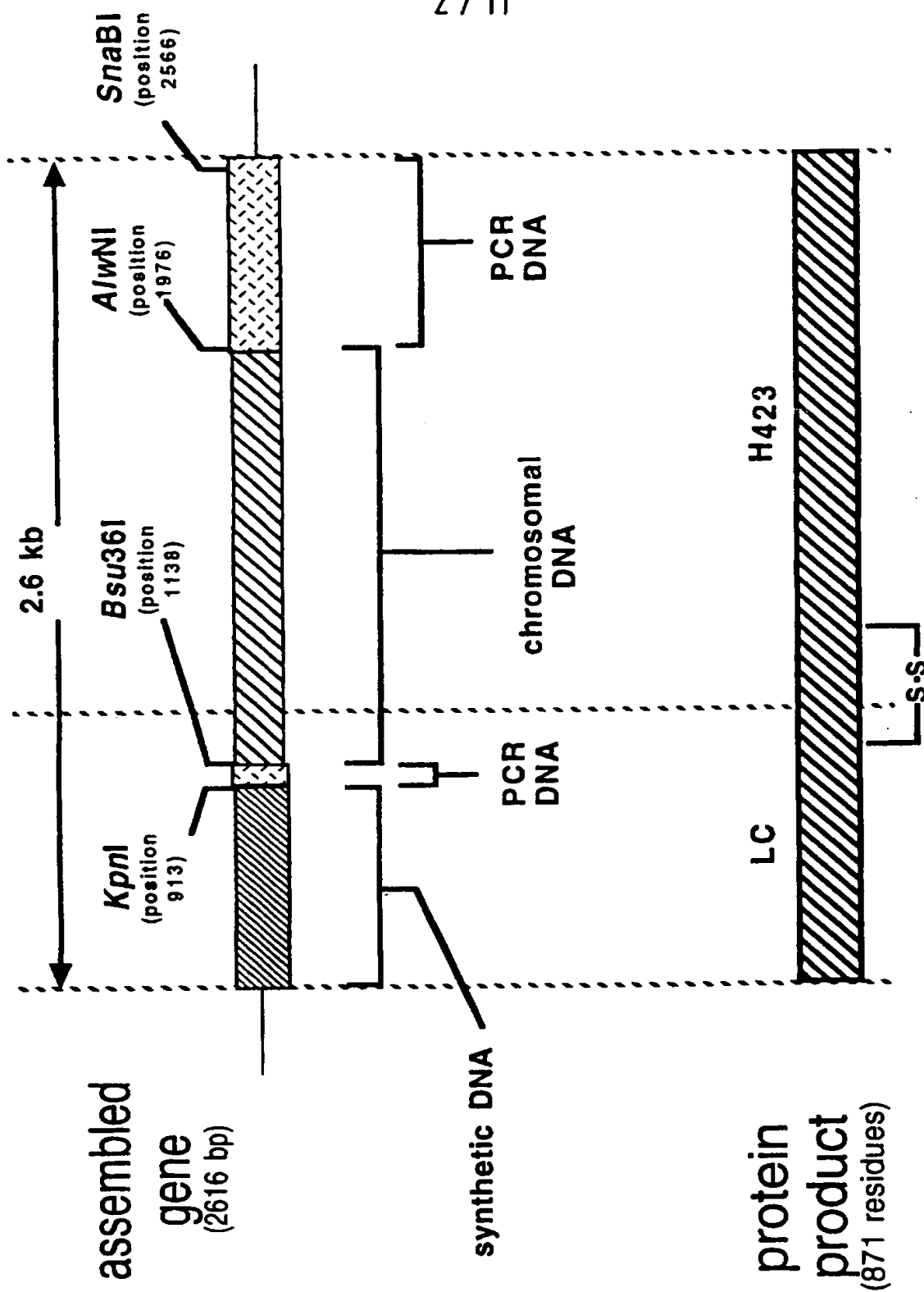


FIG. 2

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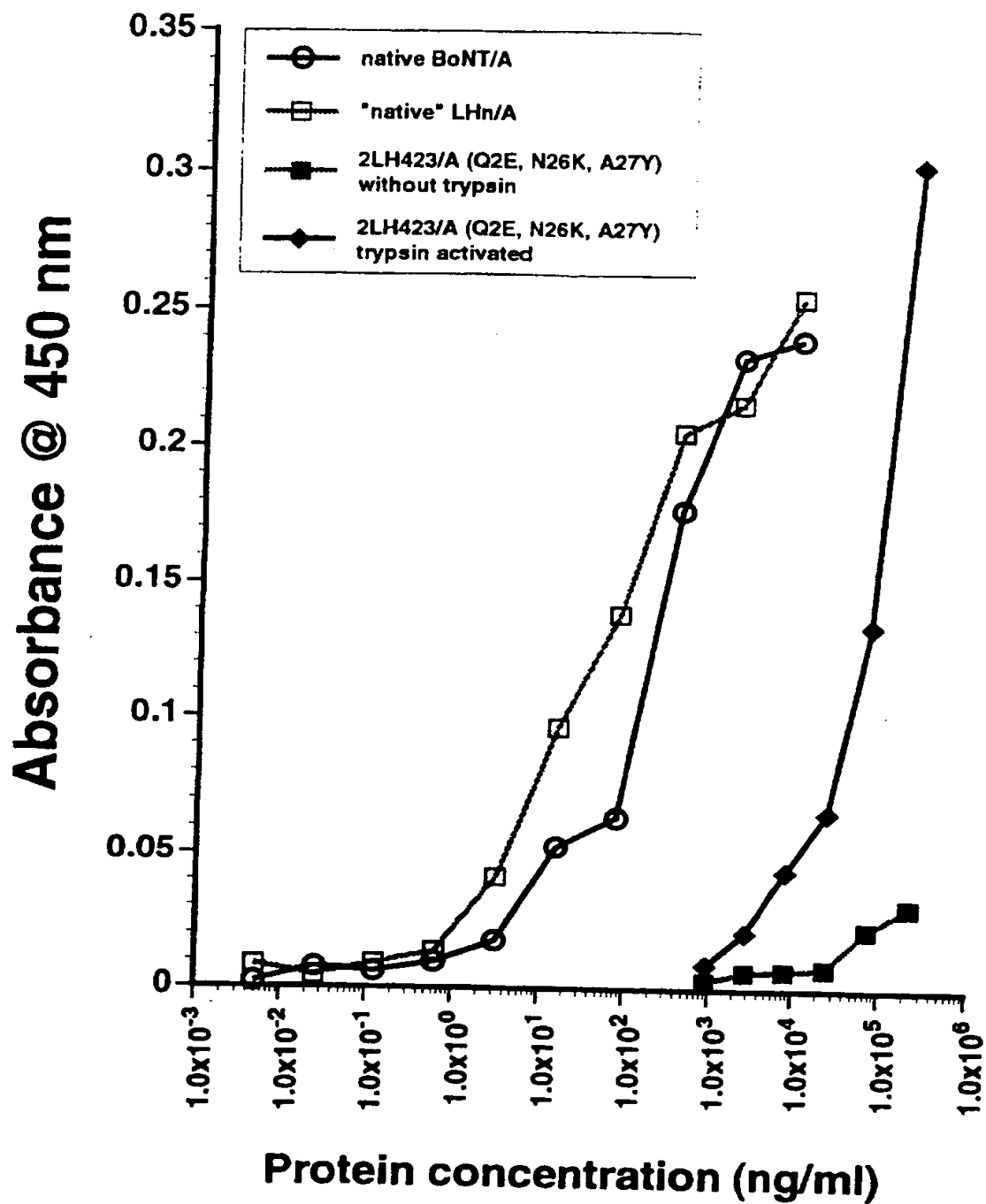
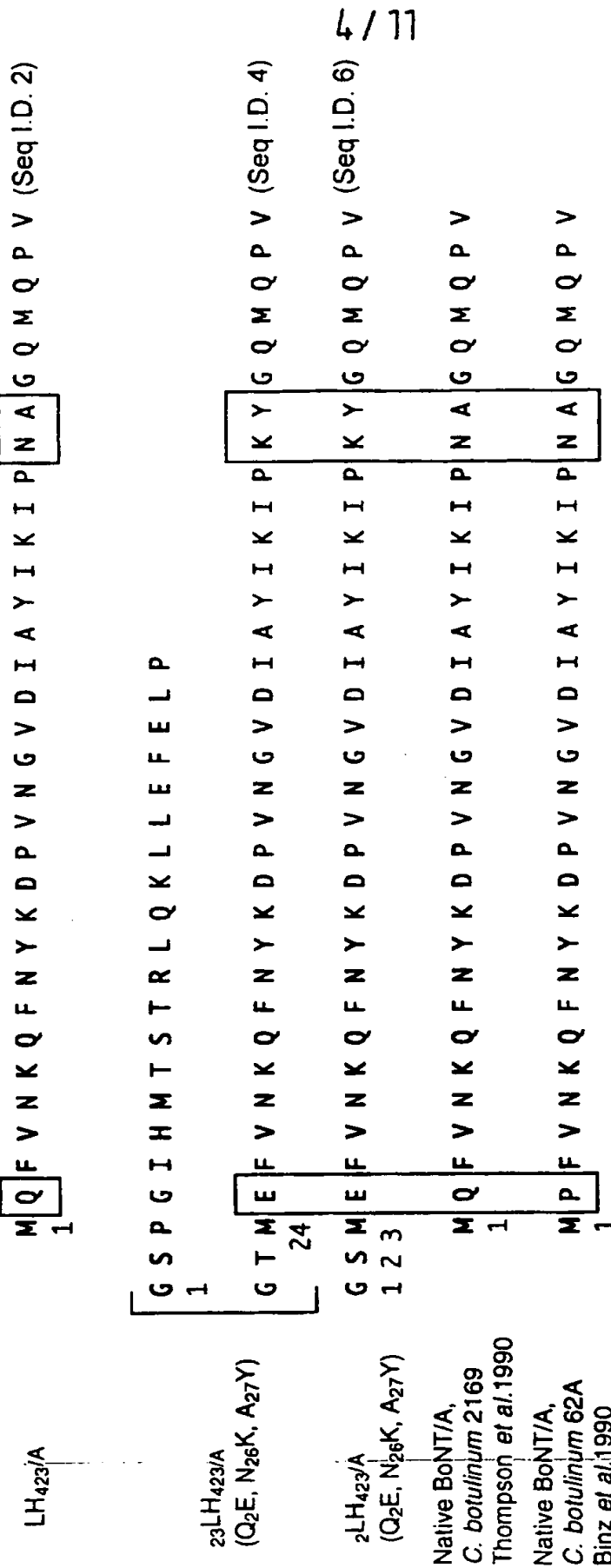


FIG. 3



 = REGIONS OF NON-IDENTITY WITH THE NATIVE SEQUENCES.

FIG. 4

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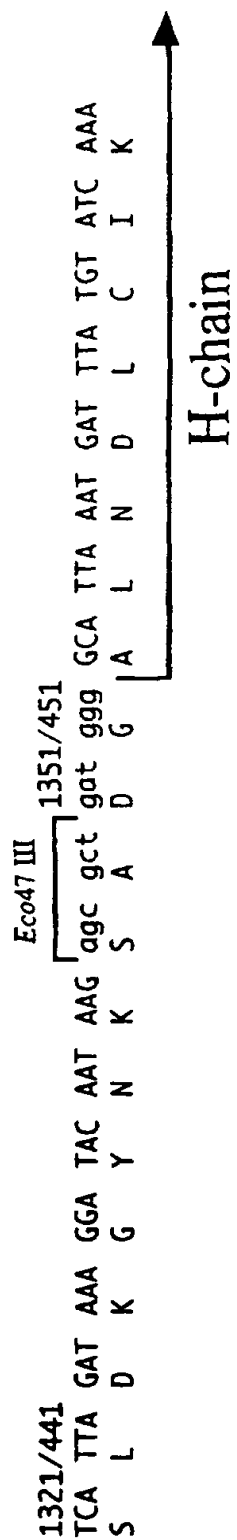


FIG. 5

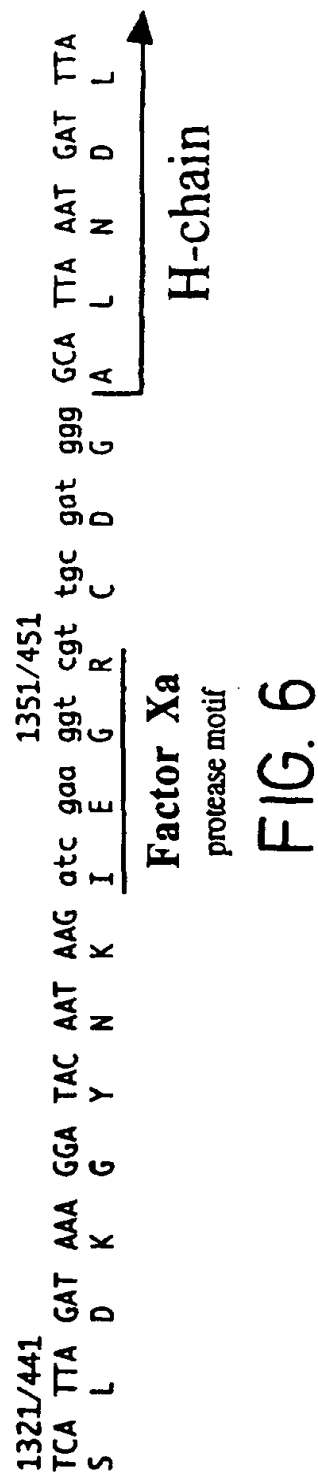


FIG. 6



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IGF-1

2587/863 TAC GTA GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TCT AGG CCT GGA  
Y V D N Q R L L S T F T E Y I K S R P G

2647/883 CCG GAG ACG CTC TGC GGG GCT GAG CTG GTG GAT GCT CTT CAG TTC GTG TGT GGA GAC AGG  
P E T L C G A E L V D A L Q F V C G D R

2707/903 GGC TTT TAT TTC AAC AAG CCC ACA GGG TAT GGC TCC AGC AGT CGG AGG GCG CCT CAG ACA  
G F Y F N K P T G Y G S S S R A P Q T

2767/923 GGT ATC GTG GAT GAG TGC TGC TTC CGG AGC TGT GAT CTA AGG AGG CTG GAG ATG TAT TGC  
G I V D E C C F R S C D L R R L E M Y C

2827/943 GCA CCC CTC AAG CCT GCC AAG TCA GCT GAA GCT TAG  
A P L K P A K S A E A stop

FIG. 7

CtxA14

2587/863 TAC GTA GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TCT AGG CCT CAA  
Y V D N Q R L L S T F T E Y I K S R P Q

2647/883 TCT AAA GTT AAA AGA CAA ATA TTT TCA GGC TAT CAA TCT GAT ATT GAT ACA CAT AAT AGA  
S K V K R Q I F S S G Y Q S D I D T H N R

2707/903 ATT AAG GAT GAA TTA TGA  
I K D E L stop

FIG. 8

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2587/863 TAC GTA GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TCA GGC CTG AAT  
 Y V D N Q R L L S T F T E E Y I K S G L N  
 2647/883 TCC CCG GGT GCA GCT CAT TAT GCG CAA CAC GAT GAA GCC GTA GAC AAC AAA TTC AAC AAA  
 S P G A A H Y A Q H D E A V D N K F N K  
 2707/903 GAA CAA AAC GCG TTC TAT GAG ATC TTA CAT TTA CCT AAC TTA AAC GAA GAA CAA CGA  
 E Q Q N A F Y E I L H L P N L N E E Q R  
 2767/923 AAC GCC TTC ATC CAA AGT TTA AAA GAT GAC CCA AGC CAA AGC GCT AAC CTT TTA GCA GAA  
 N A F I Q S L K D D P S Q S A N L L A E  
 2827/943 GCT AAA AAG CTA AAT GAT GCT CAG GCG CCG AAA GTA GAC AAC AAA TTC AAC AAA GAA CAA  
 A K K L N D A Q A P K V D N K F N K E Q  
 2887/963 CAA AAC GCG TTC TAT GAG ATC TTA CAT TTA CCT AAC TTA AAC GAA GAA CAA CGA GCC  
 Q N A F Y E I L H L P N L N E E Q R N A  
 2947/983 TTC ATC CAA AGT TTA AAA GAT GAC CCA AGC CAA AGC GCT AAC CTT TTA GCA GAA GCT AAA  
 F I Q S L K D D P S Q S A N L L A E A K  
 3007/1003 AAG CTA AAT GAT GCT CAG GCG CCG AAA GTA GAC TAG  
 K L N D A Q A P K V D \*

FIG. 9

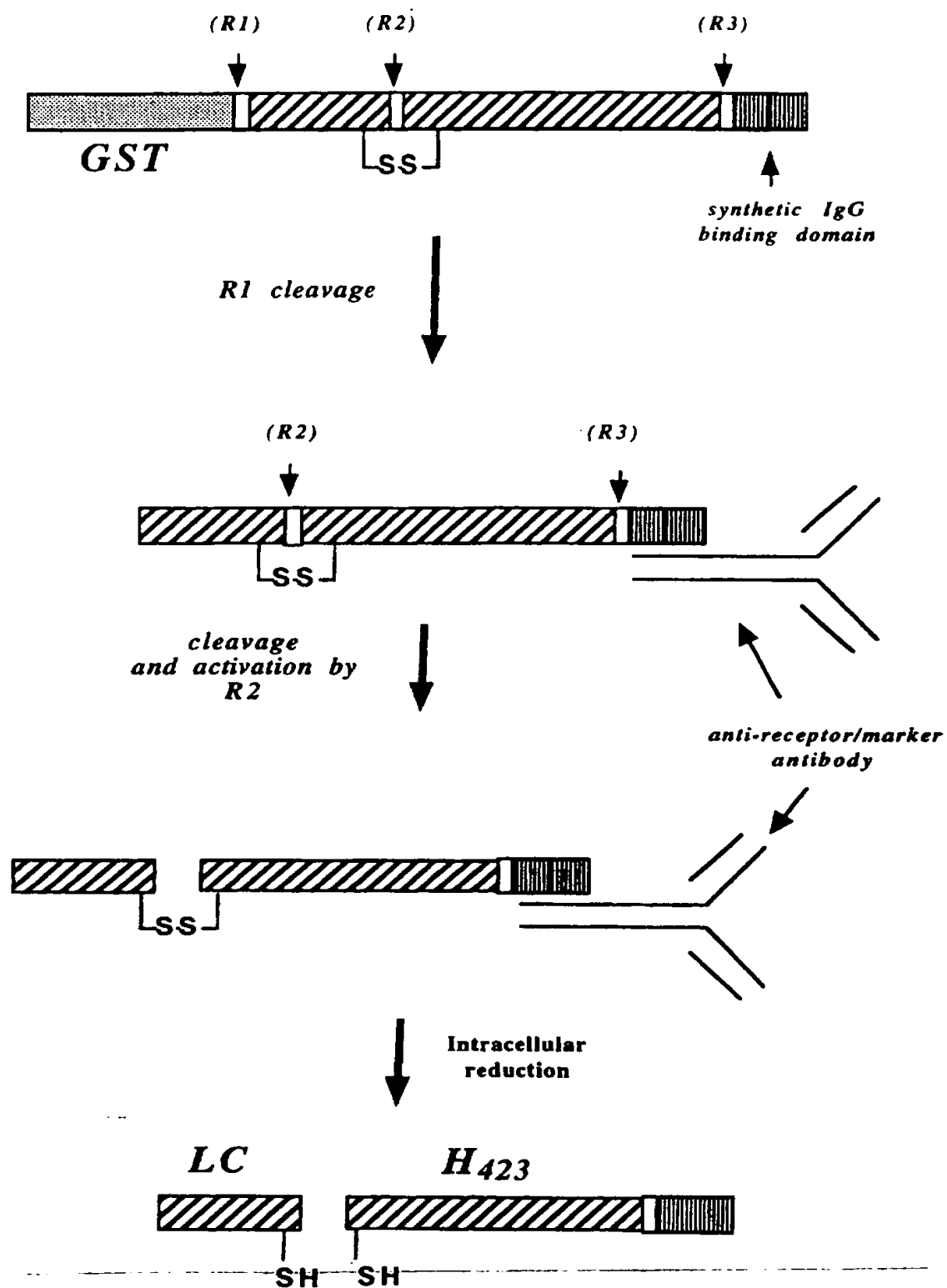
8 / 11  
LH<sub>423</sub>/A

FIG. 10

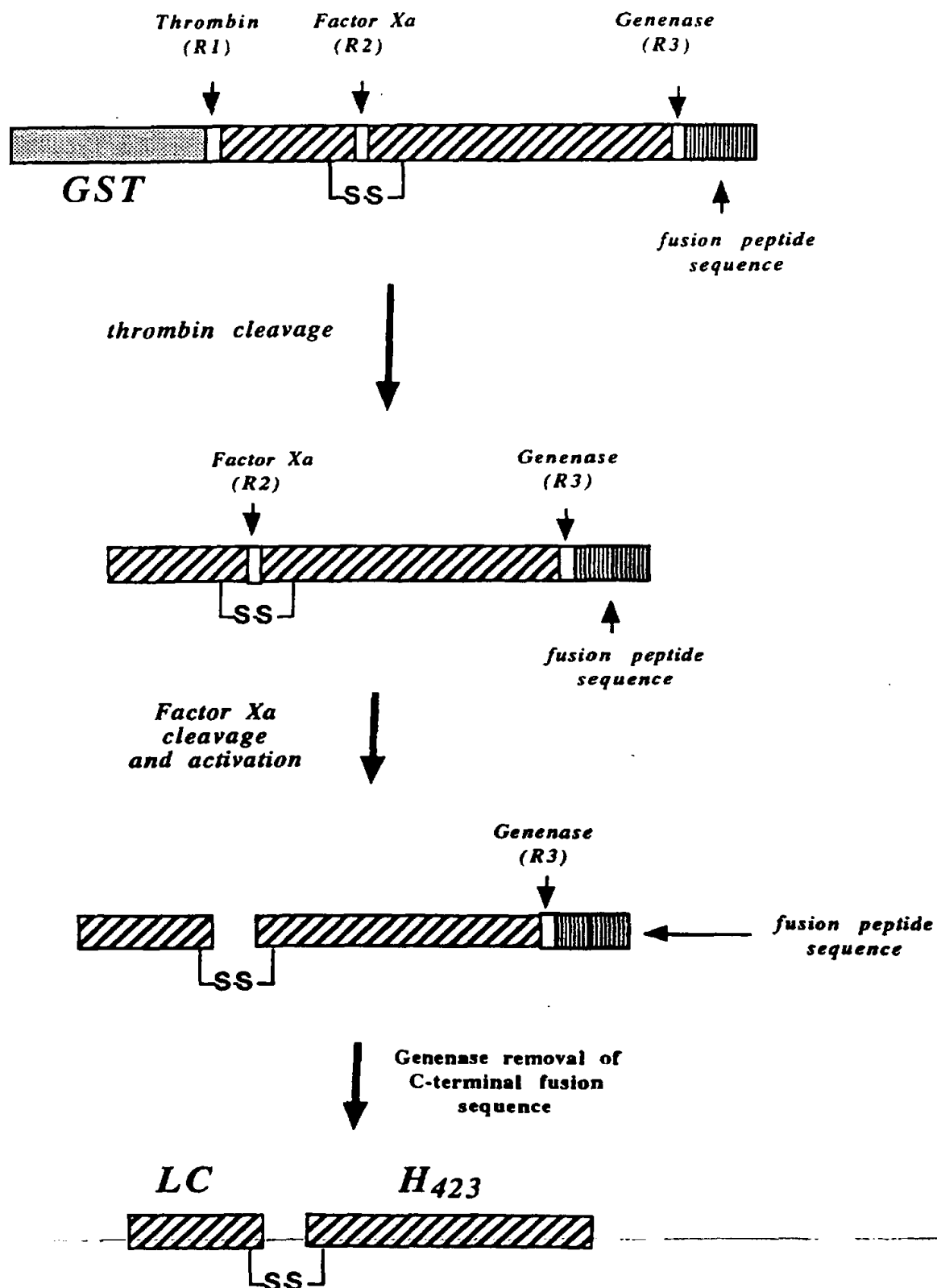
LH<sub>423</sub>/A<sup>9/11</sup>

FIG. 11

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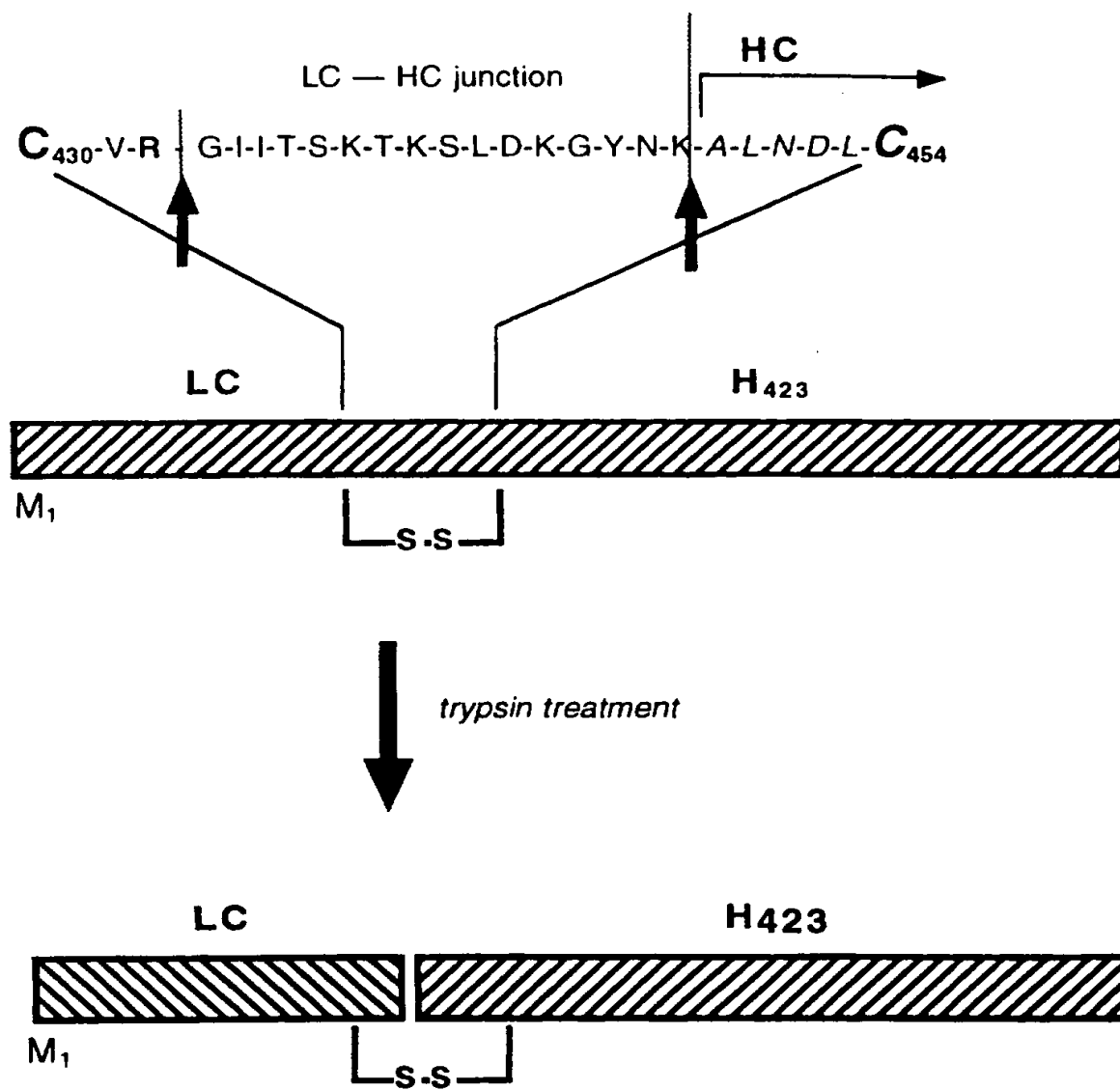


FIG. 12

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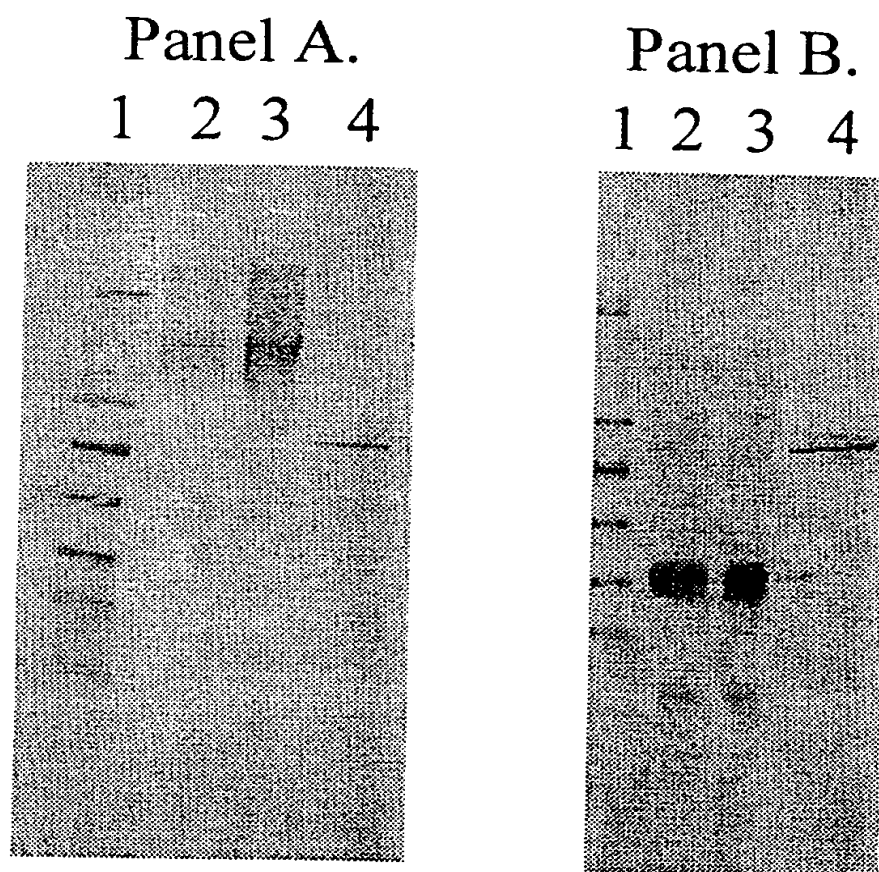


FIG. 13

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 97/02273

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/31 C12N1/21 C12P21/02 C07K14/33 A61K38/16  
A61K39/08

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C12P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 12802 A (OPHIDIAN PHARM INC ; WILLIAMS JAMES A (US); PADHYE NISHA V (US); KI) 2 May 1996 see the whole document ---	1-52
X	KURAZONO H ET AL: "Minimal essential *domains* specifying toxicity of the *light* *chains* of tetanus toxin and botulinum neurotoxin type A." J BIOL CHEM, JUL 25 1992, 267 (21) P14721-9, UNITED STATES, XP002047910 see table II --- -/--	1-52

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"A" document member of the same patent family

Date of the actual completion of the international search

9 December 1997

Date of mailing of the international search report

30. 01. 98

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Hillenbrand, G

# INTERNATIONAL SEARCH REPORT

Inter. Application No.

PCT/GB 97/02273

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LI ET AL: "A SINGLE MUTATION IN THE RECOMBINANT LIGHT CHAIN OF TETANUS TOXIN ABOLISHES ITS PROTEOLYTIC ACTIVITY AND REMOVES THE TOXICITY SEEN AFTER RECONSTITUTION WITH NATIVE HEAVY CHAIN" BIOCHEMISTRY, vol. 33, no. 22, 1994, pages 7014-7020, XP002015938 see the whole document</p> <p style="text-align: center;">---</p>	1
A	<p>BINZ T ET AL: "THE COMPLETE SEQUENCE OF BOTULINUM NEUROTOXIN TYPE A AND COMPARISON WITH OTHER CLOSTRIDIAL NEUROTOXINS" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 265, no. 16, 5 June 1990, pages 9153-9158, XP002009348 see the whole document</p> <p style="text-align: center;">-----</p>	1,26,35



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/02273

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		AU 638786 B	08-07-93
		AU 6895191 A	31-05-91
		EP 0498854 A	19-08-92
		WO 9106306 A	16-05-91
		US 5443976 A	22-08-95
		US 5340923 A	23-08-94
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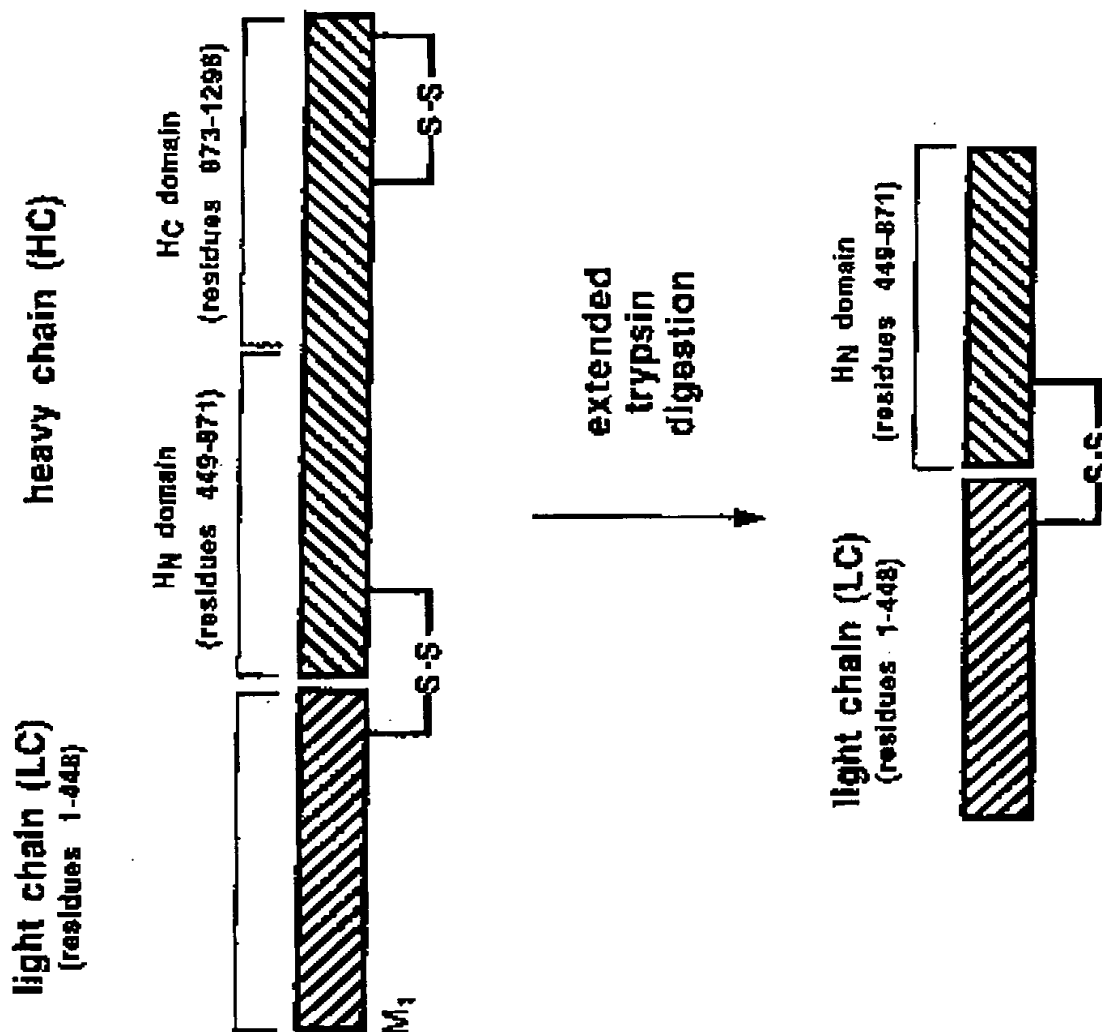


FIG. 1

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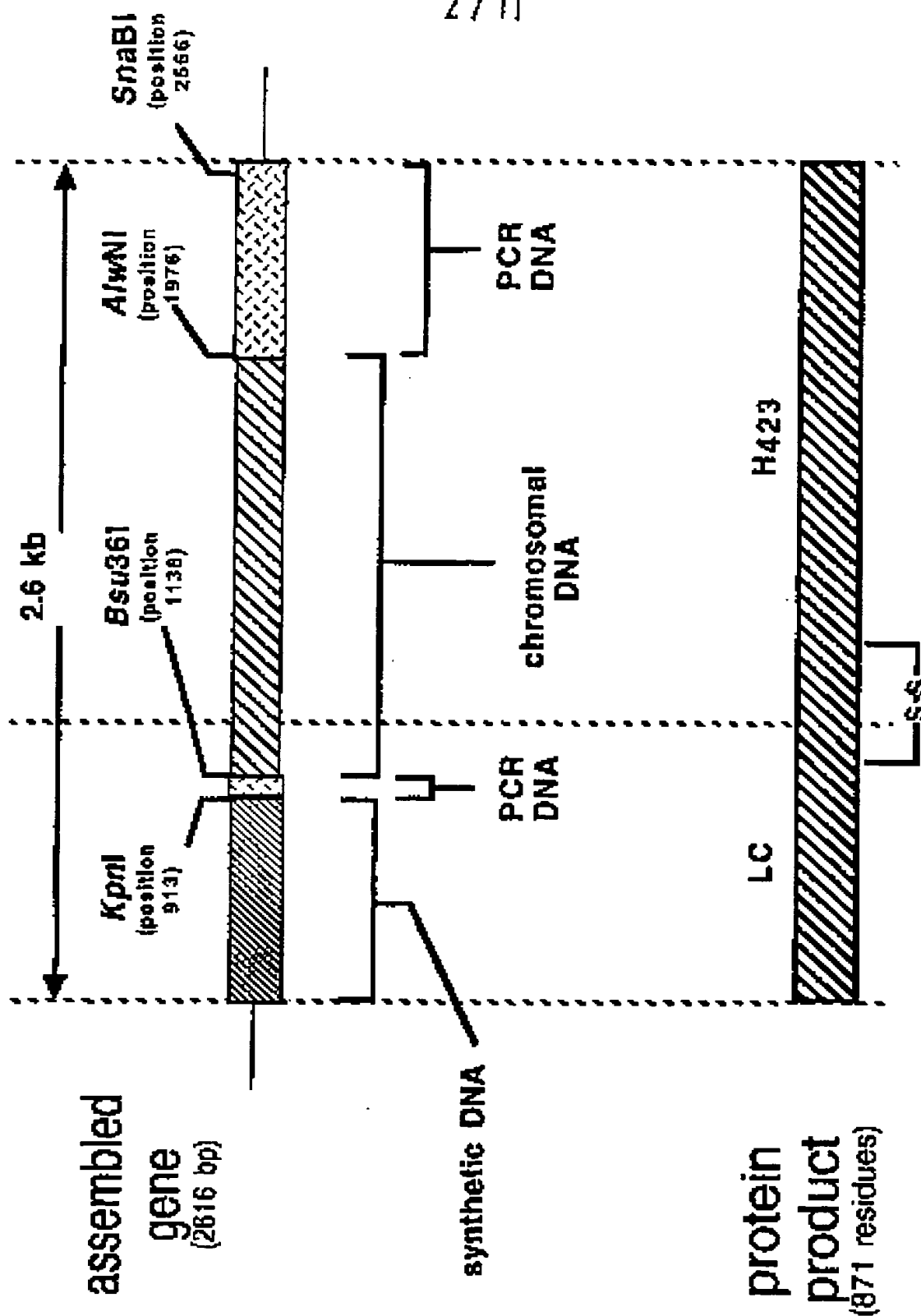


FIG. 2

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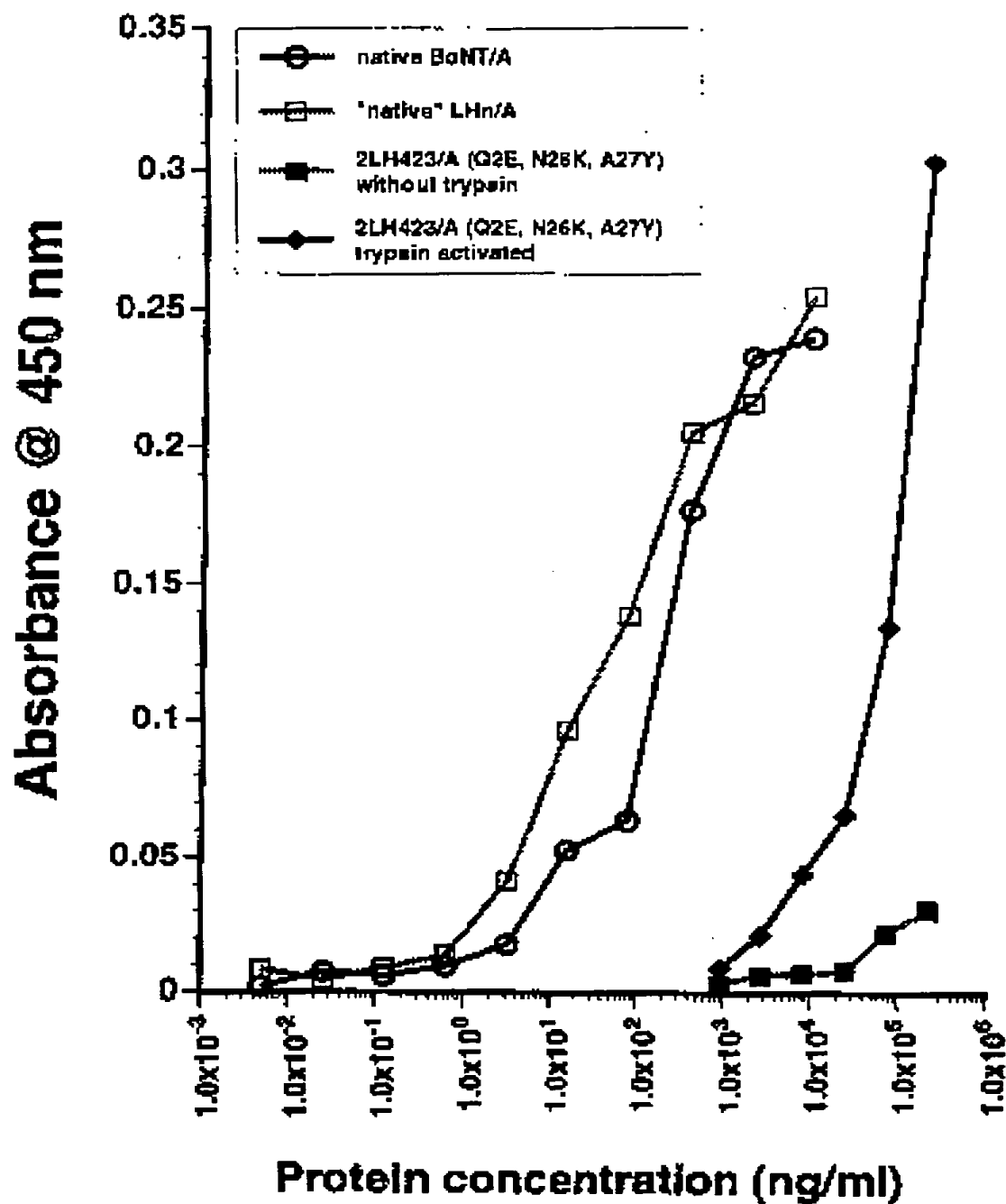
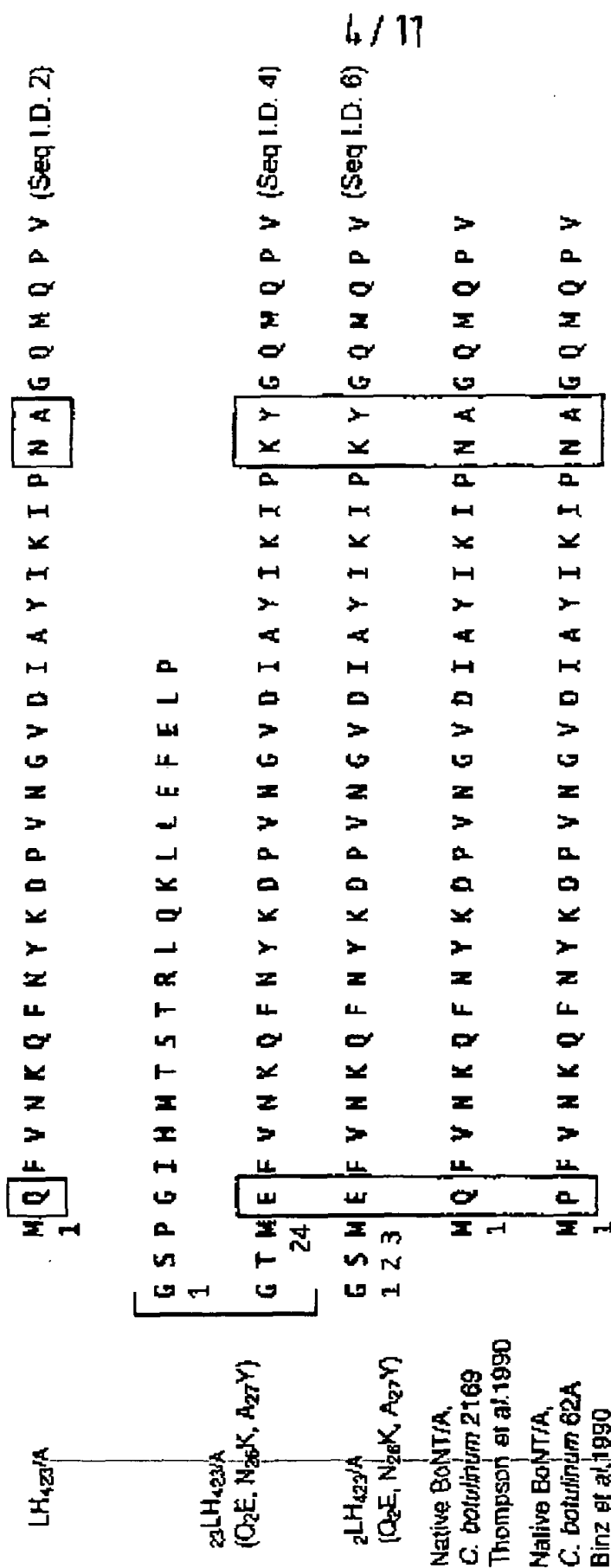


FIG. 3



□ = REGIONS OF NON-IDENTITY WITH THE NATIVE SEQUENCES.

FIG. 4

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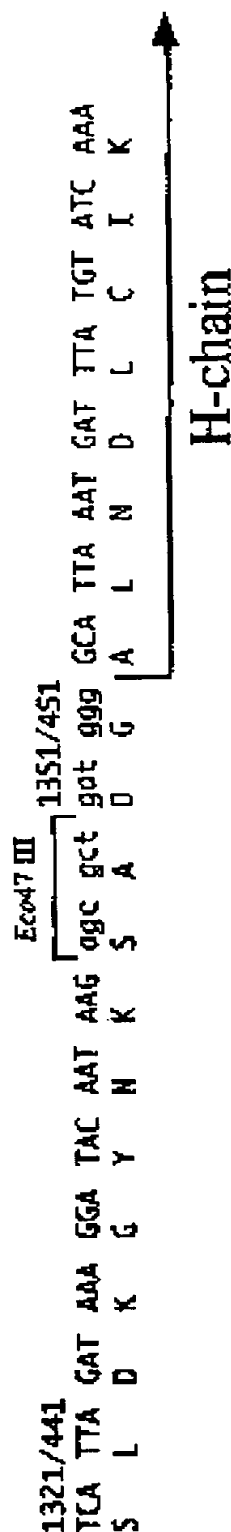


FIG. 5

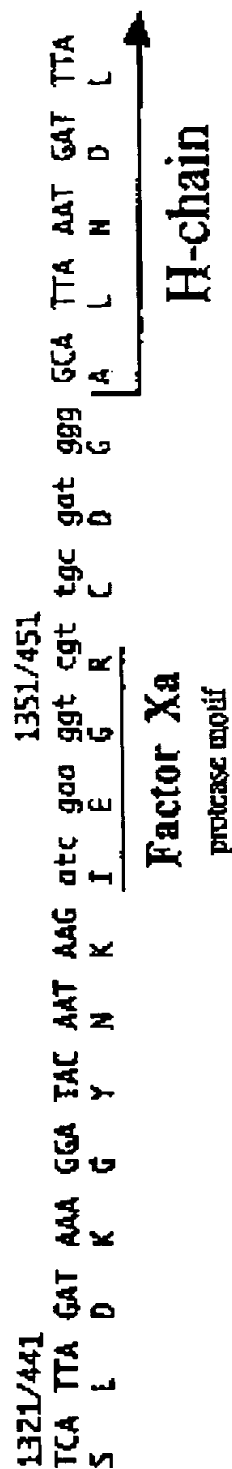


FIG. 6

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2587/863 IGF-1  
 TAC GTA GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TCT AGG CCT GGA  
 Y V D N Q R L L S T F T E Y I K S R P G  
 2647/883  
 CCG GAG ACG CTC TGC GGG GCT GAG CTG GTG GAT GCT CTT CAG TTC GTG TGT GGA GAC AGG  
 P E T L C G A E L Y D A L Q F Y C G D R  
 2707/903  
 GGC TTT TAT TTC AAC AAG CCC ACA GGG TAT GGC TCC AGC AGT CGG AGG GCG CCT CAG ACA  
 G F Y F N K P T G Y G S S S R R A P Q T  
 2767/923  
 GGT ATC GTG GAT GAG TGC TGC TTC CGG AGC TGT GAT CTA AGG AGG CTG GAG ATG TAT TGC  
 G I V D E C C F R S C D L R R L E M Y C  
 2827/943  
 GCA CCC CTC AAG CCT GCC AAG TCA GCT GAA GCT TAG  
 A P L K P A K S A E A stop

FIG. 7

2587/863 CtxA14  
 TAC GTA GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TCT AGG CCT CAA  
 Y V D N Q R L L S T F T E Y I K S R P Q  
 2647/883  
 TCT AAA GTT AAA AGA CAA ATA TTT TCA GGC TAT CAA TCT GAT ATT GAT ACA CAT AAT AGA  
 S K V K R Q I F S G Y Q S D I D T H N R  
 2707/903  
 ATT AAG GAT GAA TTA TGA  
 I K D E L stop

FIG. 8



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2587/863  
 TAC GTA GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TCA GGC CTG AAT  
 Y V D N Q R L L S T F T E Y I K S G L N  
 2647/883  
 TCC CCG GGT GCA GCT CAT TAT GCG CAA CAC GAT GAA GCC GTA GAC AAC AAA TTC AAC AAA  
 S P G A A H Y A Q H D E A V D N K F N K  
 2707/903  
 GAA CAA CAA AAC GCG TTC TAT GAG ATC TTA CAT TTA CCT AAC TTA AAC GAA GAA CAA CGA  
 E Q Q N A F Y E I L L H L P N L N E E Q R  
 2767/923  
 AAC GCC TTC ATC CAA AGT TTA AAA GAT GAC CCA AGC CAA AGC GCT AAC CTT TTA GCA GAA  
 N A F I Q S L K D D P S Q S A N L L A E  
 2827/943  
 GCT AAA AAG CTA AAT GAT GCT CAG GCG CCG AAA GTA GAC AAC AAA TTC AAC AAA GAA CAA  
 A K K L N D A Q A P K V D N K F N K E Q  
 2887/963  
 CAA AAC GCG TTC TAT GAG ATC TTA CAT TTA CCT AAC TTA AAC GAA GAA CAA CGA AAC GCC  
 Q N A F Y E I L H L P N L N E E Q R N A  
 2947/983  
 TTC ATC CAA AGT TTA AAA GAT GAC CCA AGC CAA AGC GCT AAC CTT TTA GCA GAA GCT AAA  
 F I Q S L K D D P S Q S A N L L A E A K  
 3007/1003  
 AAG CTA AAT GAT GCT CAG GCG CCG AAA GTA GAC TAG  
 K L N D A Q A P K V D •

FIG. 9

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LH<sub>423</sub>/A

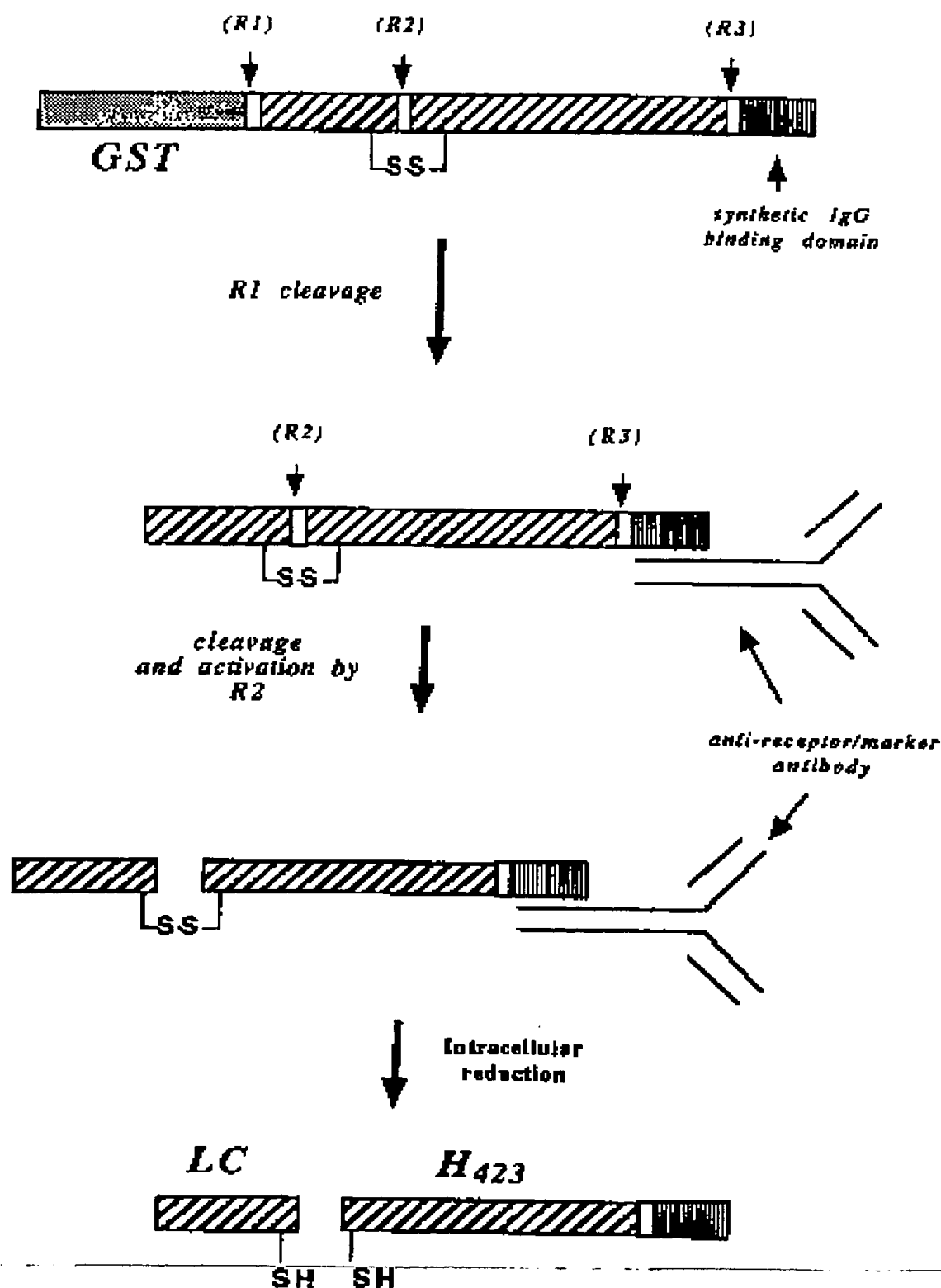


FIG. 10

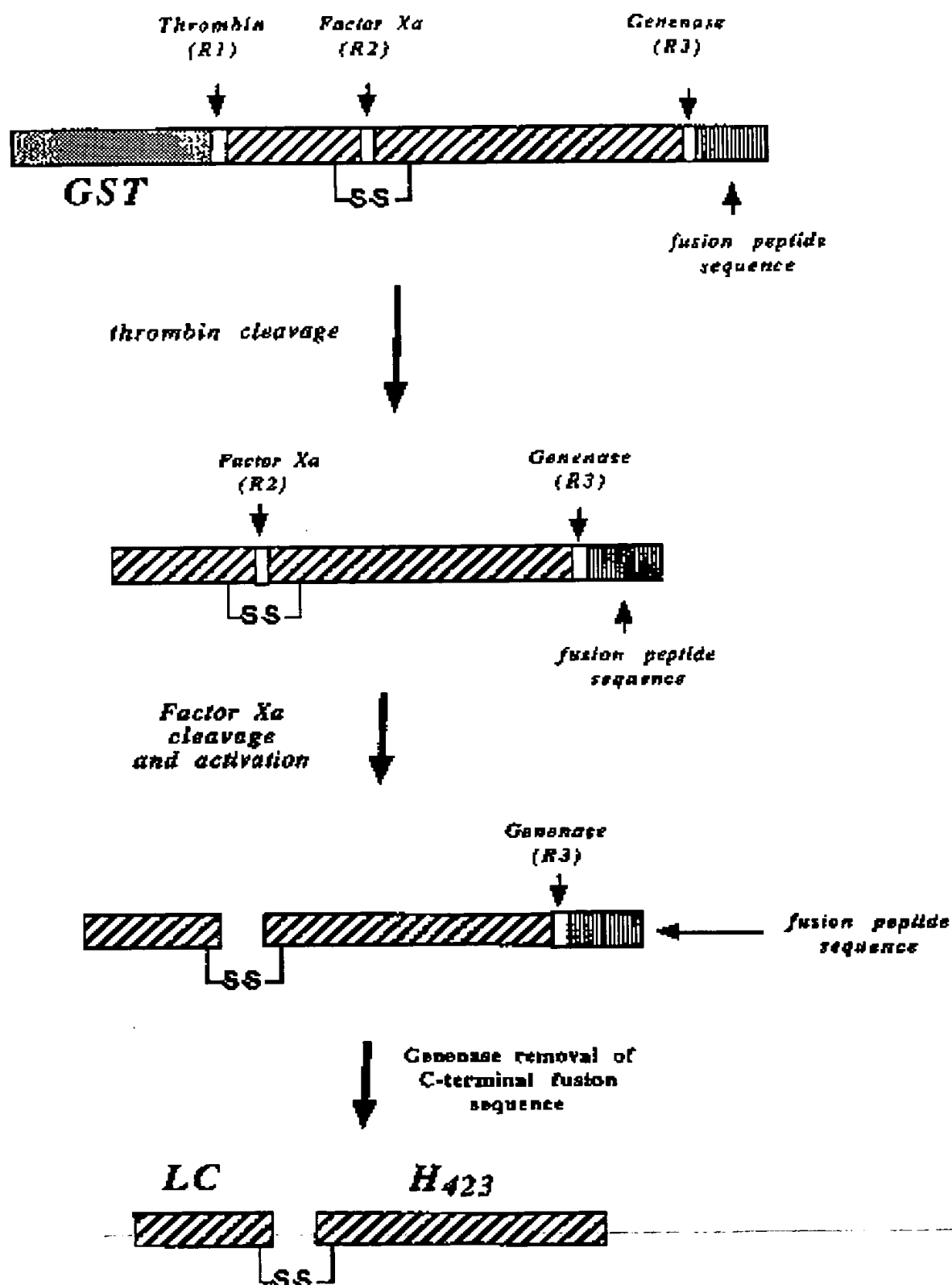
LH<sub>423</sub>/A<sup>9/11</sup>

FIG. 11

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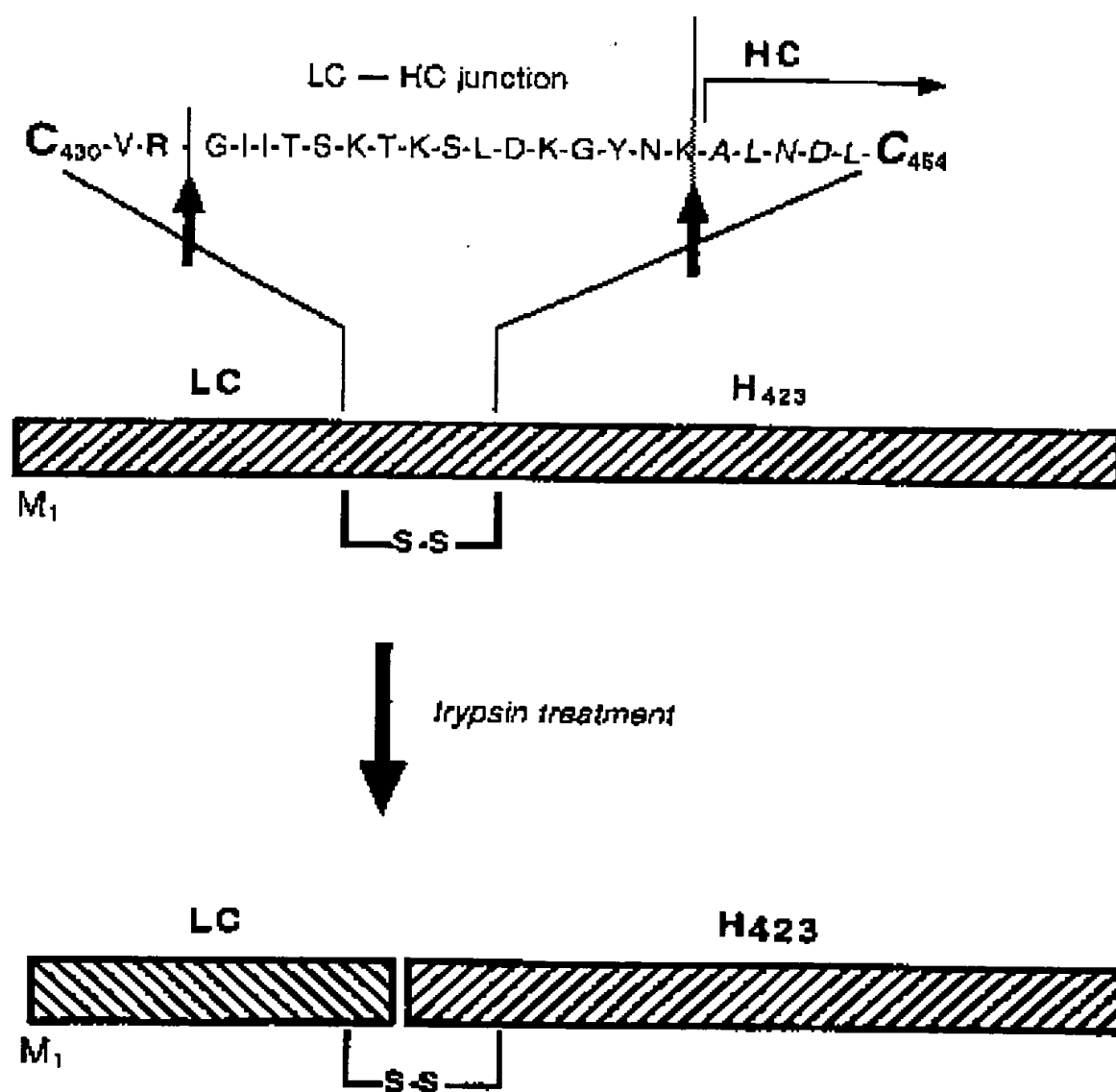


FIG. 12

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Panel A.

1 2 3 4



Panel B.

1 2 3 4

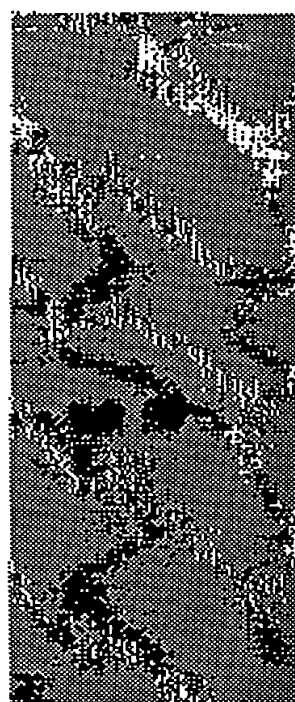


FIG. 13

